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Colour flow Doppler mapping in the assessment of prosthetic valve regurgitation

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SUMMARY Two hundred Carpentier-Edwards, Björk-Shiley, and Starr-Edwards prostheses in 173 patients were examined. Sixteen (16%) in the aortic and 24 (25%) in the mitral position were associated with clinical signs of regurgitation. A phased array system (Hewlett-Packard A77020A) with a 2·5 MHz duplex and 1·9 MHz continuous wave transducer was used. Colour flow mapping showed trivial transvalvar regurgitation in 23 (53%) metal aortic prostheses, and only nine (20%) metal mitral prostheses. This difference was probably attributable to shielding of the left atrium by the metal components. Colour mapping confirmed abnormal regurgitation in all aortic prostheses with early diastolic murmurs, but regurgitation was also shown in 25 (29%) with no diastolic murmur. Abnormal mitral regurgitation was found in 13 (54%) patients with a pansystolic murmur, but also in six (8%) with no systolic murmur. Two patients, thought on clinical grounds to have mild mitral regurgitation, had unexpectedly large jets on colour flow mapping. About one in three prostheses had paraprosthetic leaks, 65 (79%) of which were small with a jet area less than 20% of the area of the receiving chamber. The development of new paraprosthetic leaks led to the diagnosis of bacterial endocarditis in two patients. In eight patients regurgitation was first diagnosed with continuous wave Doppler, but was afterwards shown with colour mapping and in a further 10 regurgitation could only be shown by continuous wave Doppler.

Colour flow mapping was less sensitive than continuous wave Doppler in detecting regurgitation, but seemed able to distinguish normal transvalvar from paraprosthetic regurgitation. Further studies in the natural course of paraprosthetic leaks and a comparison of the transoesophageal and transthoracic approaches in the assessment of mitral prostheses are needed.

It is important to be able to detect and localise the site of regurgitation associated with prosthetic valves. The development of a new leak in a paraprosthetic position may suggest bacterial endocarditis or in a transvalvar position may be the first indication of primary failure in a bioprosthesis. It is also useful to be able to guide the surgeon when repair of a paraprosthetic leak is required.

Continuous wave Doppler ultrasound is highly sensitive for the detection of regurgitation, but it cannot pinpoint the leak. Although localisation is possible with conventional pulsed Doppler, it is time consuming and of limited accuracy.[1-3] Colour flow Doppler mapping gives a cross sectional version of conventional pulsed Doppler. Velocity and directional information are collected at multiple depths down each scan line and are then superimposed on a cross sectional echocardiographic image in real time. Colour flow Doppler mapping is highly sensitive for detecting regurgitation in native valves,[4 5] but there are no published studies of its application in the assessment of regurgitation associated with prosthetic valves.

The aim of this study was to establish the role and likely benefits of colour flow Doppler mapping in assessing the incidence, severity, and localisation of regurgitant jets in prosthetic valves.

Patients and methods

PATIENTS

Consecutive patients with prosthetic valves referred either for routine echocardiography or with suspected prosthetic regurgitation were studied from 1 December 1986 to 30 March 1988. Patients with tricuspid valve prostheses or aortic and mitral prostheses other than Carpentier-Edwards, Björk-

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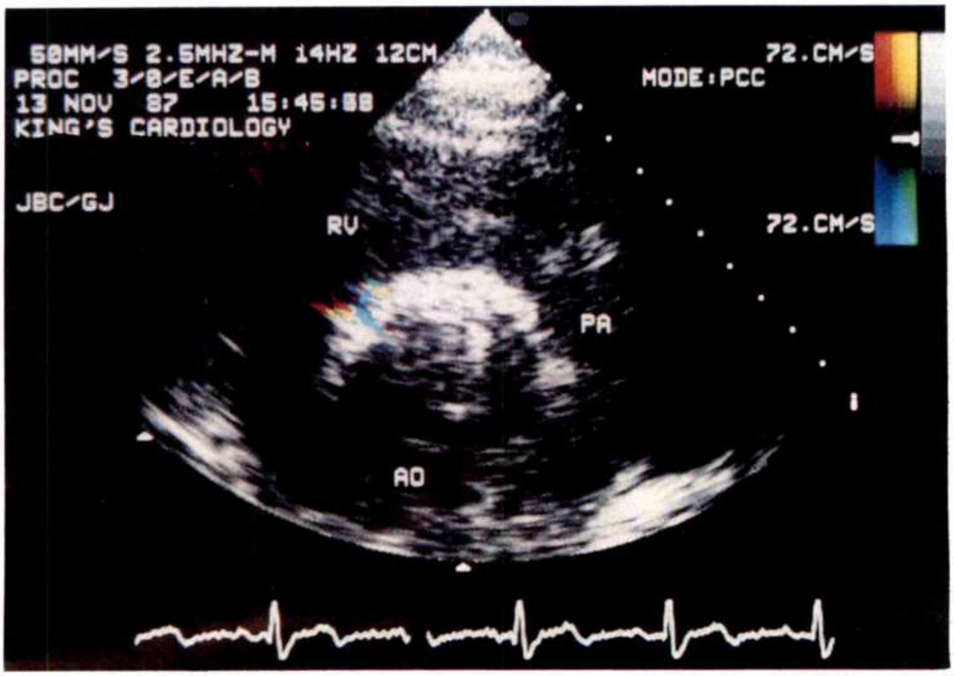

Fig 1 *Paraprosthetic aortic regurgitation. Parasternal short axis view of a Starr-Edwards aortic prosthesis. The base of the jet was clearly seen in the anterior part of the sewing ring at about 11 o'clock.*

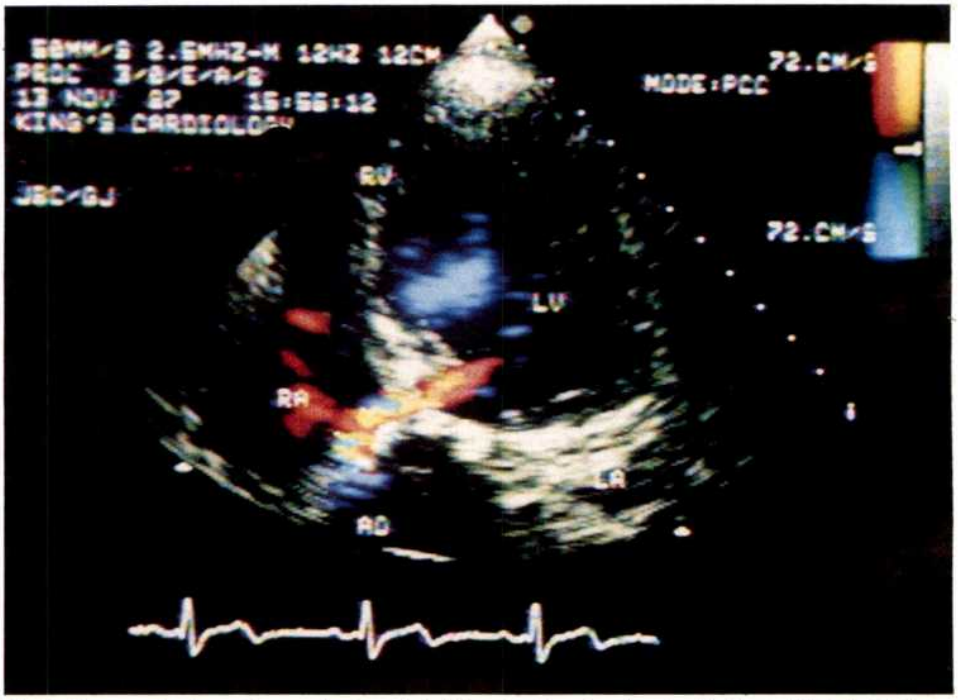

Fig 2 *Paraprosthetic aortic regurgitation. Apical five chamber view showing the Starr-Edwards aortic prosthesis in fig 1. A stream of colour originated in the aortic root and was seen passing around the sewing ring and into the left ventricle.*

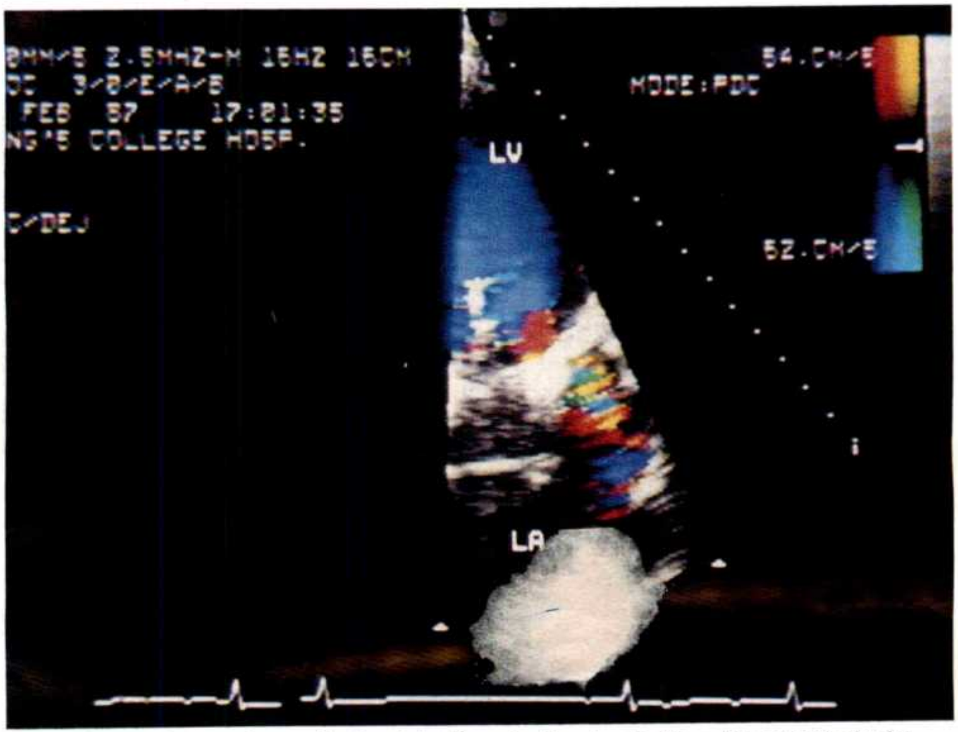

Fig 3 *Paraprosthetic aortic regurgitation. Apical four chamber view of a Starr-Edwards mitral valve. Flow acceleration (red) was seen within the left ventricle at the edge of the sewing ring. There was a mitral regurgitant jet in the left atrium, but no clear stream of colour around the prosthesis.*

Shiley, or Starr-Edwards were excluded because there were too few of them. This left 200 prostheses in 173 patients. There were 103 aortic prostheses in which 16 (16%) had the murmur of aortic regurgitation and 97 mitral prostheses of which 24 (25%) had pansystolic murmurs.

APPARATUS

We used a phased array ultrasound system (Hewlett-Packard A77020A) with a 1·9 MHz continuous wave Doppler probe and a duplex 2·5 MHz transducer for imaging and colour flow Doppler mapping. The colour flow Doppler system was set to maximum packet size and minimum reject with the gain just below the level at which ambiguous colour flooding occurred. Both enhanced and variance threshold maps were used. Recordings were made on to professional quality three quarter inch U-matic tape.

STUDY

A clinical examination was performed to look for evidence of prosthetic dysfunction or coexistent tricuspid regurgitation. Cross sectional imaging with colour flow Doppler was then performed in all conventional approaches and in addition the transducer was tilted in an attempt to detect areas of abnormal flow in more anterior and posterior positions. The parasternal short axis view was found to be particularly useful for localising aortic jets (fig 1). A continuous wave examination was then performed from the apical approach with multiple gain settings and angulations. If a regurgitant jet was shown for the first time on continuous wave Doppler a second attempt was made to detect it by colour flow Doppler mapping.

Regurgitation was considered to be paraprosthetic if: (*a*) a stream of colour was visible around the sewing ring in mitral prostheses during systole and in aortic prostheses during diastole (fig 2); (*b*) the origin of the regurgitant jet was visible at a point outside the sewing ring although there was no visualisation of flow around the valve (fig 3); (*c*) the origin of the regurgitant jet was in the region of the sewing ring and although not clearly outside the ring, was separate from forward flow (fig 4).

Regurgitation was considered to be transvalvar if: (*a*) its origin was seen within the orifice (as defined by the forward flow pattern) in at least two different views (fig 5); (*b*) in metal mitral prostheses systolic retrograde flow was seen originating at the edge of the

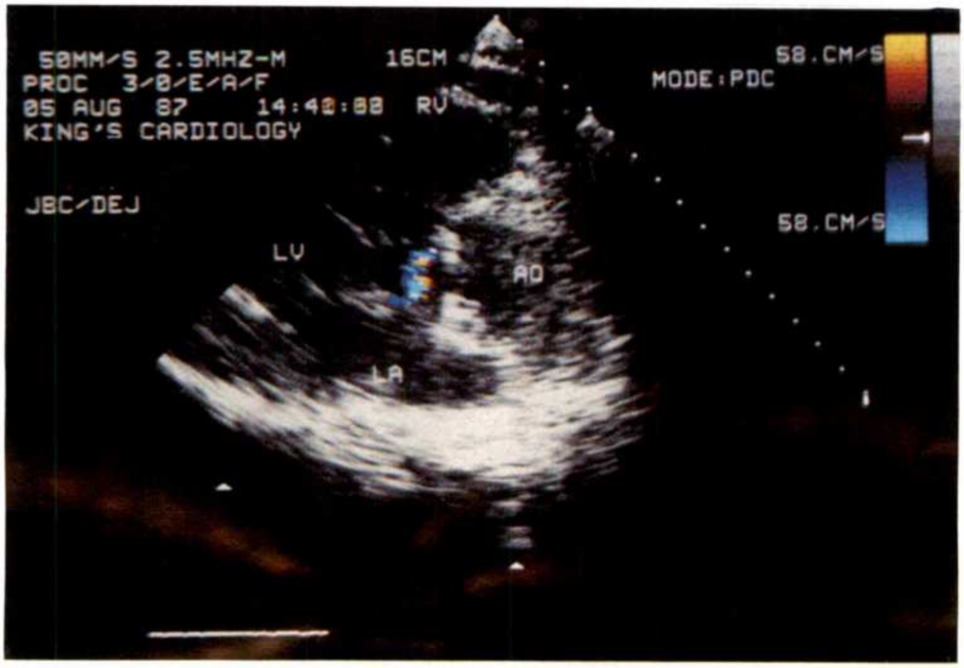

Fig 4 *Paraprosthetic aortic regurgitation. Parasternal long axis view of a Björk-Shiley prosthesis. The origin of the jet is separate from forward flow.*

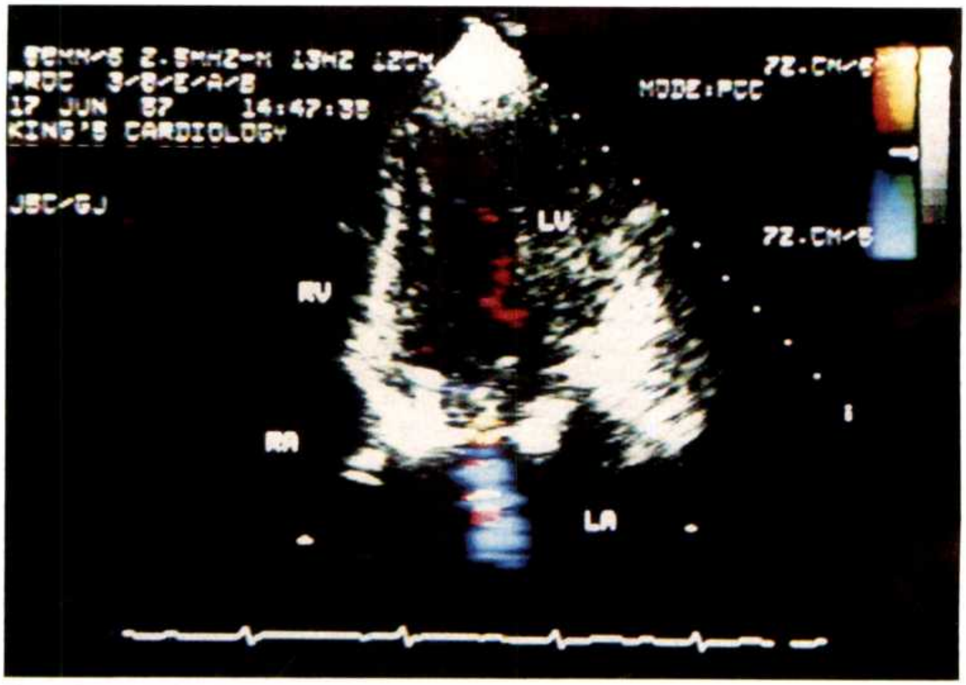

Fig 5 *Regurgitation through a mitral prosthesis. An apical four chamber view of a Carpentier-Edwards prosthesis. The jet also appeared inside the valve ring in the parasternal long axis view.*

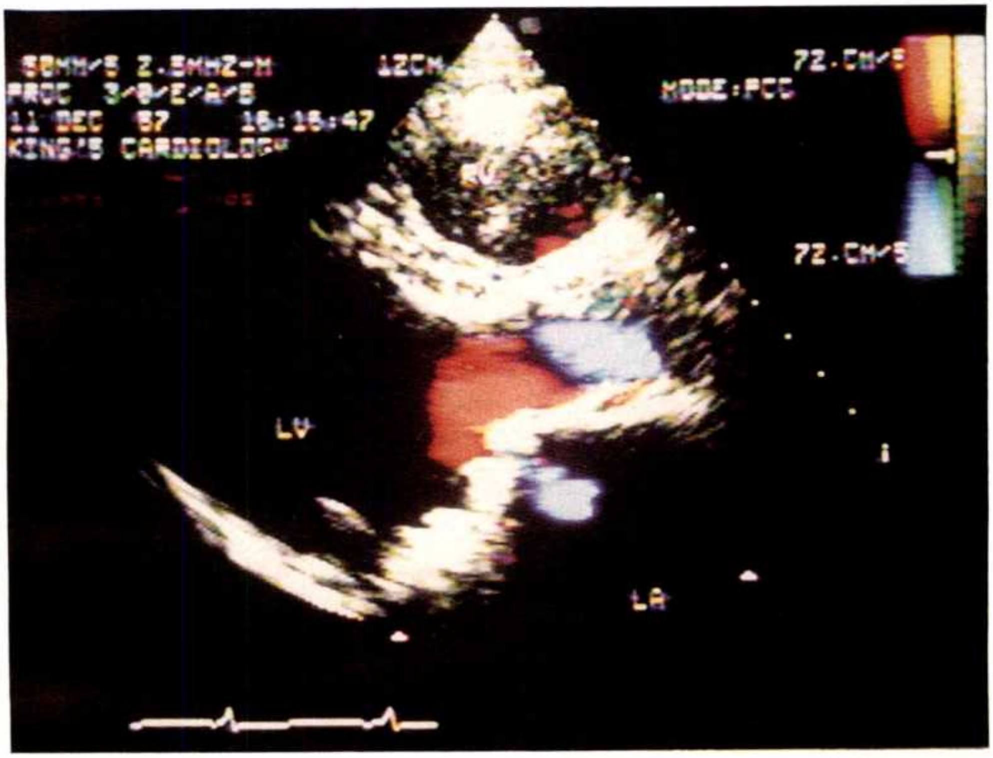

Fig 6 *Parasternal long axis view of transvalvar regurgitation. A high velocity jet was recorded by continuous wave. On colour flow Doppler mapping, there was high velocity flow (blue) between the disc and the sewing ring continuous with a billowing low velocity jet seen within the left atrium in systole.*

occluder (disk or ball) in the parasternal long axis view (fig 6); or (*c*) beyond the shielding of the occluder in the absence of evidence of a paraprosthetic leak.

The severity of paraprosthetic aortic regurgitation was estimated from the arc occupied by the base of the jet around the sewing ring. The maximum area of the aortic or paraprosthetic mitral jet was also expressed as a percentage of the receiving chamber area[6] when the approach that gave optimal imaging of the jet was used. A semiquantitative estimate of jet area in transmitral regurgitation was not attempted because of shielding by the metal components.

Five patients with severe prosthetic dysfunction were evaluated by cardiac catheterisation and contrast injection—four proceeded to operation. One further patient had an operation without previous catheterisation and four cases had catheterisation for coronary artery disease and the prosthesis was also evaluated at this time.

Results

INCIDENCE OF REGURGITATION

Regurgitation was detected in 97 (49%) prostheses (table 1). Trivial transvalvar regurgitation was shown more commonly in the Björk-Shiley (63%) than the Starr-Edwards (27%) prostheses in the aortic position, but in similar frequencies in the mitral position. Paraprosthetic leaks occurred in 73% Starr-Edwards aortic prostheses, in 6% Carpentier-Edwards mitral prostheses, and in 21–28% of Starr-Edwards mitral, Carpentier-Edwards aortic, Björk-Shiley mitral, and Björk-Shiley aortic. Of the 12 Carpentier-Edwards prostheses with transvalvar regurgitation, all but one had been in position for longer than 48 months (mean 77 (29) months). Of those with paraprosthetic regurgitation, eight (40%) had been in position for less than 12 months. It was impossible to localise the site of regurgitation in one Carpentier-Edwards prosthesis where the base of the jet was broad.

Aortic regurgitation was confirmed in all prostheses with an early diastolic murmur, but mild paraprosthetic regurgitation was also found in a further 25 (29%) of 87 patients with no murmur. Of the 24 cases with pansystolic murmurs, 13 (54%) had mitral regurgitation and in the others only tricuspid regurgitation was found. One mitral prosthesis with a high pitched ejection systolic murmur had minor regurgitation originating at the base of one cusp.

Table 1 *Occurrence of regurgitation shown by ultrasound (percentages in parentheses)*

	Carpentier-Edwards		*Björk-Shiley*		*Starr-Edwards*	
	AVR (n = 60)	*MVR (n = 53)*	*AVR (n = 32)*	*MVR (n = 29)*	*AVR (n = 11)*	*MVR (n = 15)*
Total frequency	23 (38)	11 (21)	30 (94)	17 (59)	10 (91)	6 (40)
PP on CFD	17 (28)	3 (6)	9 (28)	6 (21)	8 (73)	4 (27)
Transvalvar on CFD	6 (10)	6 (11)	20 (63)	7 (24)	3 (27)	2 (13)
PP and transvalvar	1 (2)	0	3 (9)	0	2 (18)	0
Uncertain	1	0	0	0	0	0
Multiple PP	1		1	1	0	0
On CW not CFD	0	2	4 (13)	4 (14)	1	0
Murmur	8 (13)	7 (13)	5 (16)	4 (14)	3 (27)	2 (13)

AVR, aortic valve replacement; CFD, colour flow Doppler; CW, continuous wave Doppler; MVR, mitral valve replacement; PP, paraprosthetic.

Two further mitral valves with new ejection murmurs had demonstrable flow acceleration in the left ventricular outflow tract thought to be related to the tip of one of the stents. Of the 73 mitral prostheses with no pansystolic murmur, six (8%) had paraprosthetic mitral regurgitation. Most cases of severe prosthetic dysfunction were suspected clinically, but in two severe paraprosthetic mitral regurgitation was shown by colour flow Doppler despite only soft pansystolic murmurs. In two patients the development of new paraprosthetic regurgitation led to the diagnosis of bacterial endocarditis. A further 11 patients with unexplained breathlessness were shown to have normal prosthetic function.

SEVERITY OF REGURGITATION (TABLE 2)

Most of the regurgitant jets were small. The area of the jet in 65 (79%) was less than 20% of the receiving chamber area. Shielding by the prosthesis precluded reliable estimation of the severity of regurgitation through metal mitral prostheses. Paraprosthetic mitral regurgitant areas were also likely to have been underestimated because of partial shielding of the jet.

The base of the aortic jet involved approximately 90° of the ring in one prosthesis, approximately 45° in eight, and <20° in the remaining 37. Table 3 shows the distribution of the jets. The jets were multiple in origin in three prostheses.

Table 2 *Severity of regurgitation*

	<10%	*10–19%*	*20–40%*	*>40%*
Aortic CE:				
PP	4	11	2	0
Through	1	3	1	1
Mitral CE.				
PP	2	1	0	0
Through	4	0	1	1
Aortic BS:				
PP	2	2	3	2
Through	13	7	0	0
Mitral BS				
PP	2	2	2	0
Aortic SE:				
PP	2	4	1	1
Through	2	1	0	0
Mitral SE·				
PP	1	1	2	0

CE, Carpentier-Edwards; BS, Bjork-Shiley, PP, paraprosthetic; SE, Starr-Edwards.

COLOUR FLOW DOPPLER COMPARED WITH CONVENTIONAL DOPPLER

All regurgitant jets shown by colour flow Doppler were also recorded by continuous wave or conventional pulsed Doppler. There were, however, 10 patients in whom low intensity regurgitant jets shown by continuous wave were not seen on colour flow Doppler. In eight further patients, regurgitation was missed with the first colour flow Doppler examination but shown at a subsequent examination.

There were 15 patients with regurgitant prostheses who had been examined by conventional Doppler ultrasound alone and in whom it had not been possible confidently to localise the jet. We thought that localisation was possible with colour flow Doppler in all of these patients.

COMPARISON WITH CATHETER OR FINDINGS AT OPERATION

Cardiac catheterisation was performed in five patients and confirmed the Doppler findings in all of them. There was mild regurgitation through a severely stenotic prosthesis in two patients and

Table 3 *Localisation of paraprosthetic regurgitant jets*

Type of valve	*Anterior*	*Posterior*	*RV side*	*LV side*
Aortic.				
CE	8	7	5	1
BS	6	1	2	1
SE	3	3	1	1
Mitral.	*Anterior*	*Posterior*	*Septal*	*Free wall*
CE	1	1	1	0
BS	4	0	1	2
SE	1	0	1	2

CE, Carpentier-Edwards; BS, Bjork-Shiley; LV, left ventricle; RV, right ventricle, SE, Starr-Edwards.

severe paraprosthetic regurgitation in three. At operation, however, one patient who was thought to have a paraprosthetic leak was found to have a sinus between the base of the cusp and the stent, but no dehiscence of the sewing ring. The colour flow findings were confirmed in the other four patients. Two patients thought to have considerable paraprosthetic regurgitation had severe intercurrent illness which prevented further intervention. Catheterisation was also performed for suspected coronary artery disease in four patients with Carpentier-Edwards prostheses; it confirmed the absence of regurgitation.

Discussion

This is the first study to use colour flow Doppler mapping to describe patterns of regurgitation in a consecutive series of patients with prosthetic valves. The striking finding was the high frequency of unsuspected paraprosthetic regurgitation in prostheses of all three types in the aortic position and in Björk-Shiley and Starr-Edwards prostheses in the mitral position.

Most of the regurgitant jets were, however, small and probably not haemodynamically important. Furthermore, most severely dysfunctioning prostheses were diagnosed clinically. Was colour flow mapping, therefore, of clinical use? Two patients with severe paraprosthetic regurgitation were first diagnosed with colour flow Doppler and in two further patients newly developed mild regurgitation led to the diagnosis of bacterial endocarditis. Localisation of the site of regurgitation guided the surgeon in all three patients with paraprosthetic leaks who underwent reoperation. In all 24 mitral prostheses where a new systolic murmur was heard after operation, colour flow mapping was able to localise the origin of the flow disturbance to the mitral or tricuspid valve or to the left ventricular outflow tract. It may be difficult clinically to exclude mitral prosthetic regurgitation in a patient with coexistent tricuspid regurgitation. Colour flow mapping also contributed by excluding significant prosthetic regurgitation in 11 patients in whom the cause of failure to improve after operation was not obvious clinically.

Paraprosthetic leaks may occur because the bed created by scraping away calcified tissue is never perfectly circular so that the prosthesis cannot always fit snugly. Regurgitation may be less common in the Carpentier-Edwards mitral prostheses because the annulus is covered in sponge and may allow a better fit than the rings of metal prostheses. The state of the recipient tissue, the type and technique of suturing, and the methods of myocardial preservation may all contribute to the development of paraprosthetic regurgitation and future studies should evaluate these prospectively.

Normally functioning Björk-Shiley and Starr-Edwards prostheses have trivial transvalvar leaks during closure. In the aortic prostheses these jets were always small, less than 20% of the receiving chamber area, and usually narrow. Twin jets were sometimes seen. Transvalvar regurgitation was seen less commonly in the mitral prostheses. In this position, access can be improved by the use of the transoesophageal approach, which allows interrogation of the left atrium without the problem of shielding. It is likely that shielding by mitral prostheses was the reason why paraprosthetic regurgitation was seen more frequently with valves in the aortic rather than the mitral position. There is, however, no published study describing the results that can be obtained with the transoesophageal approach and how often clinically important information gained by this route is missed by the transthoracic approach. Most studies with conventional Doppler reported lower incidences of regurgitation than shown here, but they were studies of small numbers.[2 7 8] A study of the functioning of Björk-Shiley prostheses by colour flow Doppler failed to find regurgitation in any of the 10 aortic prostheses examined.[9] The fact that we detected regurgitation in 63% of aortic prostheses probably reflects the increased sensitivity of the apparatus that we used.

There is uncertainty about whether any regurgitation through Carpentier-Edwards prostheses can be regarded as normal. Conventional ultrasound showed regurgitation in 8–26% of aortic prostheses[8 10 11] and in 4–11% of mitral prostheses.[10 11] We found valvar regurgitation in 10% of the aortic and 11% of the mitral valves. Only one regurgitant prosthesis had been in position for less than 48 months; this suggests that transvalvar regurgitation is a sign of primary failure.

Systematic validation with angiography of the localisation of regurgitation by colour Doppler mapping is not a practical proposition. Furthermore, angiography may be less accurate than Doppler ultrasound[3] and it is possible that colour flow Doppler mapping will soon be considered the reference standard for localisation. In one case in this series a leak at the base of the cusp was wrongly diagnosed as being paraprosthetic. This emphasises that colour flow Doppler mapping may not always reliably distinguish between eccentric jets through a prosthesis and paraprosthetic leaks. When abnormal flow is clearly seen around the sewing ring it is unlikely that mistakes can be made.

The area of the regurgitant jet shown by colour flow Doppler is dependent on gain and instrument settings[12 13] and may not always give an accurate assessment of the severity of regurgitation. Helmcke *et al*, however, have shown a good correlation between the angiographically assessed severity and mitral regurgitant jet area expressed as a percentage of left atrial area.[14] Most patients with mild regurgitation by angiographic criteria had regurgitant areas of less than 20% and most with severe regurgitation had areas over 40%.

We conclude that colour flow Doppler mapping detects most expected and abnormal regurgitant jets, most of which are small and probably not haemodynamically important. Occasionally, however, they are more severe than had been suspected on clinical grounds. New paraprosthetic leaks suggest the possibility of bacterial endocarditis. The technique is useful for the localisation of new murmurs appearing after mitral valve replacement and probably for excluding important valve dysfunction. Further studies of the natural course of paraprosthetic regurgitation and comparative studies of the transoesophageal and transthoracic approaches in the assessment of prostheses should now be undertaken.

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Aortic valve replacement with combined myocardial revascularisation

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SUMMARY Early and late outcome was studied in 630 patients who underwent aortic valve replacement between 1974 and 1982. Group 1 (506 patients) did not have important coronary artery disease, group 2 (69 patients) had coronary artery disease and underwent coronary artery bypass grafting, and group 3 (55 patients) had coronary artery disease but did not undergo myocardial revascularisation. Early mortality (within 30 days of operation) was significantly lower for group 1 (6%) than for group 2 (13%) and for group 3 (16%). Operative mortality in all three groups was lower in patients operated on more recently. The three year survival of patients in group 1 (83%) was significantly higher than that of patients in group 3 (62%) but not than that of patients in group 2 (76%).

The findings of this study suggest that the presence of coronary artery disease increases the risk of aortic valve replacement whether or not coronary artery grafting is performed. Myocardial revascularisation, however, seems to return patients with aortic valve and coronary artery disease to a survival curve similar to that of patients with isolated aortic valve disease.

Since 1960 when Harken *et al* first performed intracardiac aortic valve replacement using a caged ball prosthesis in the subcoronary position,[1] isolated aortic valve replacement has become well established and is routinely practised both for the relief of symptoms and to improve prognosis. The role of additional coronary artery bypass grafting in patients found to have coronary artery disease is, however, less certain. A review of the results of combined aortic valve replacement and coronary artery grafting in several centres shows more variable early mortality than that seen after isolated aortic valve replacement.[2 3]

There are several important questions to consider in the management of patients with aortic valve disease. Firstly, in patients who have clinical evidence of important aortic valve dysfunction we need to define which group of patients should undergo coronary angiography at the time of cardiac catheterisation. The second question is the definition of the group of patients who should undergo combined valve replacement and coronary bypass surgery. The mere demonstration of coronary artery disease does not necessarily indicate surgical treatment. Although coronary artery grafting in patients with coronary artery disease is a good treatment for symptoms, it improves long term survival in only some patients.[4-6] It may be that only in those patients with coronary artery disease of similar severity to that in patients in whom long term survival is improved will bypass grafting improve long term survival. Thirdly, what is the best surgical approach in this group of patients? Myocardial protection is made difficult both by the mass of ventricular muscle at risk during aortic cross clamping and by the presence of obstructive coronary arterial lesions. The combination of aortic valve surgery and coronary artery surgery should only be performed together if mortality and morbidity are low and there is a demonstrable long term improvement in symptoms and/or survival.

Most of these questions can only be investigated by the analysis of uncontrolled retrospective data. We have studied some of these questions in patients who had combined aortic valve disease and coronary artery disease. The place of surgery for isolated aortic valve disease is already well defined.

Patients and methods

PATIENTS

We reviewed the records of the 630 patients who underwent aortic valve replacement between January

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1974 and December 1982 at the Regional Cardiac Centre, Wythenshawe Hospital. The patients did not have important dysfunction of the other heart valves. Coronary arteriography was performed on 571 (91%) patients and 125 patients were found to have important coronary artery disease[4] (> 50% reduction of intraluminal diameter of a major coronary artery).

Three groups of patients were identified. Group 1 consisted of 506 patients who had aortic valve disease but no evidence of important coronary artery disease. Group 2 consisted of 69 patients who had aortic valve disease and coronary artery disease and who underwent coronary artery surgery. The remaining 55 patients (group 3) had combined aortic valve disease and coronary artery disease, but did not undergo coronary artery bypass grafting.

On the basis of clinical findings and catheterisation data, patients were categorised as having aortic stenosis (peak systolic pressure gradient $\geqslant$50 mm Hg), aortic incompetence (greater than 2/4 as assessed from the aortogram by two experienced observers), or mixed aortic valve disease. Left ventricular function was assessed from the left ventricular angiogram by two experienced observers who estimated the left ventricular ejection fraction as poor (< 30%), moderate (30–70%), or good (> 70%). The angiograms of all patients who underwent coronary arteriography were reviewed by at least two experienced observers.

OPERATIVE TECHNIQUE

Between 1974 and 1982, the period of this review, operative technique has changed. Aortic valve replacement is performed under standard cardiopulmonary bypass at moderate systemic hypothermia (28°C). Before the widespread use of cardioplegia, the aorta was cross clamped and the heart was cooled topically by the technique described by Shumway *et al*[7]; a left ventricular vent was routinely used. If additional coronary artery grafting was carried out, distal anastomoses were constructed after valve replacement with the heart fibrillating, and the proximal anastomoses with the heart beating.

Currently, the aortic valve is replaced under cardioplegic arrest. For isolated valve replacement additional topical cooling is maintained by a cooling jacket around the heart. In combined aortic valve and saphenous vein bypass surgery, slush is applied to the arrested heart and the valve is excised. The distal anastomoses are then constructed, and finally the valve is replaced and proximal anastomoses are completed after closure of the aorta, with the heart beating.

A mechanical valve was used for 90% of patients in group 1, 88% of patients in group 2, and 89% of patients in group 3. The remaining patients had tissue valves. All patients with mechanical valves were on long term anticoagulant treatment, whereas anticoagulants were stopped after three months in patients with tissue valves.

Table 1 *Clinical details of patients in group 1, group 2, and group 3*

	Group 1 (n = 506)	*Group 2 (n = 69)*	*Group 3 (n = 55)*
Mean (SD) age (years)	51 (13)*	58 (7)	61 (7)
Valve lesion:			
Aortic stenosis	171 (34%)	18 (26%)	23 (42%)
Aortic incompetence	218 (43%)	28 (41%)	19 (35%)
Mixed	117 (23%)	23 (33%)	13 (23%)
NYHA.			
I	233 (46%)	14 (20%)**	27 (49%)
II	46 (9%)	11 (16%)**	5 (9%)
III	207 (41%)	40 (58%)**	21 (38%)
IV	20 (4%)	4 (6%)**	2 (4%)
Angina:			
Yes	233 (46%)	55 (80%)**	27 (49%)
No	273 (54%)	14 (20%)**	28 (51%)

Group 1, patients who underwent aortic valve replacement; group 2, patients who underwent aortic valve replacement and coronary artery surgery; group 3, patients with coronary artery disease who underwent aortic valve replacement only.
*Significantly different from group 2 and group 3 (p < 0 01).
**Significantly different from group 1 and group 3 (p < 0 01).

STATISTICAL ANALYSIS

We examined group differences by a one way analysis of variance and compared proportions by the χ^2 test.

Actuarial survival curves were calculated by standard life table analysis techniques.[8]

Results

Table 1 shows the clinical details and table 2 the results of cardiac catheterisation. The patients who had important coronary artery disease (groups 2 and 3) were significantly older (p < 0·01) than patients in

Table 2 *Coronary angiographic findings and left ventricular function in group 2 and group 3*

	Group 2† (n = 69)	*Group 3† (n = 55)*
Coronary artery disease:		
1 vessel		
Left anterior descending	12*	18
Circumflex	1*	7
Right	10*	10
2 vessel	19*	16
3 vessel	17*	2
Left main stem stenosis	10*	2
Mean no. grafts/patient	1 5	0
Ejection fraction:		
Poor (< 30%)	22%	27%
Moderate (30–70%)	47%	42%
Good (> 70%)	31%	31%

*Significantly different from group 3 (p < 0 01)
†See footnote to table 1 for definitions.

Table 3 *Early mortality of patients in group 1, group 2, and group 3 between 1974 and 1978 and between 1979 and 1982*

	Group 1† *(n = 506)*	*Group 2†* *(n = 69)*	*Group 3†* *(n = 55)*
1974–1978.			
No of patients undergoing operation	208	19	16
Early mortality	23 (11%)	5 (26%)	4 (25%)
1979–1982:			
No of patients undergoing operation	298	50	39
Early mortality	9 (3%)	4 (8%)	5 (13%)
Overall early mortality	6%*	13%	16%

*Significantly different from group 2 and group 3 (p < 0·01).
†See footnote to table 1 for definitions

group 1. There was no significant difference in the nature of the aortic valve lesion between the three groups of patients. More patients in group 2 had angina before operation than groups 1 and 3 (p < 0·01). Twenty six per cent of patients who experienced angina had important coronary artery disease compared with 13% of those who did not have angina.

Of the patients who had coronary artery disease, those who underwent coronary artery bypass grafting (group 2) had more severe coronary disease (p < 0·01) and were in a worse functional state before operation (p < 0·01) than those who did not undergo coronary artery surgery (group 3). There was no significant difference, however, in preoperative left ventricular function between group 2 and group 3. Preoperative left ventricular function in the patients with coronary artery disease was not significantly different from that of patients in group 1; 23% poor, 44% moderate, and 33% good (table 2). The overall early (within 30 days of operation) mortality for the three groups of patients was 6% for group 1, 13% for group 2, and 16% for group 3. Early mortality was significantly lower (p < 0·01) in group 1 than in group 2 and group 3. Table 3 shows the reduction in operative mortality of patients operated on more recently. The overall early mortality for patients who had cardioplegia for myocardial protection was 6·6% (4·2% (18/428) in group 1, 13·2% (9/68) in group 2, and 17·6% (9/51) in group 3). The overall early mortality for patients who did not receive cardioplegia was 16·9% (17·9% (14/78) in group 1, 0% (0/1) in group 2, and 0% (0/4) in group 3).

Table 4 *Proportion of patients who required haemodynamic support postoperatively and incidence of perioperative myocardial infarction in group 2 and group 3*

	Group 2† *(n = 69)*	*Group 3†* *(n = 55)*
Haemodynamic support postoperatively	26%	27%
Perioperative myocardial infarction*	17%	15%

*Development of new Q wave >0·04 s.
†See footnote to table 1 for definitions.

Seven of the nine early deaths in group 2 were caused by a low cardiac output and failure to wean from cardiopulmonary bypass. Of the remaining two deaths one was caused by pancreatitis in relation to a low cardiac output state and one occurred ten days after operation in a man who had undergone aortic valve replacement and a single right coronary artery graft, and at necropsy the artery was found to be blocked.

There were nine early deaths in group 3. Seven of these were caused by low cardiac output and failure to wean from cardiopulmonary bypass. One occurred at 21 days in a patient who had persistent infection after three valve replacements for infective endocarditis, and the other was a man who underwent emergency surgery and died 21 days after operation of myocardial failure. There was only one early death in the 35 patients in group 3 who had single vessel disease while eight deaths occurred in the 20 patients who had two (or three) vessel disease or left main stem stenosis.

After operation, some patients required either inotropic infusions or placement of an intra-aortic

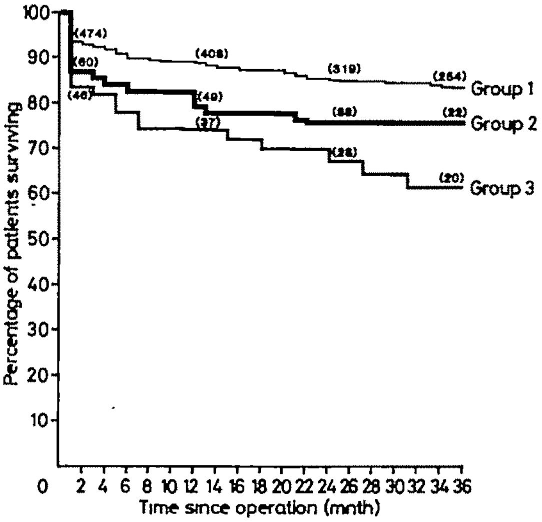

Fig 1 *Actuarial survival curve for the three groups of patients. Group 1, patients who underwent aortic valve replacement; group 2, patients who underwent aortic valve replacement and coronary artery surgery; group 3, patients with coronary artery disease, who underwent aortic valve replacement only. Figures in parentheses indicate the number of patients in each group entering that particular follow up period.*

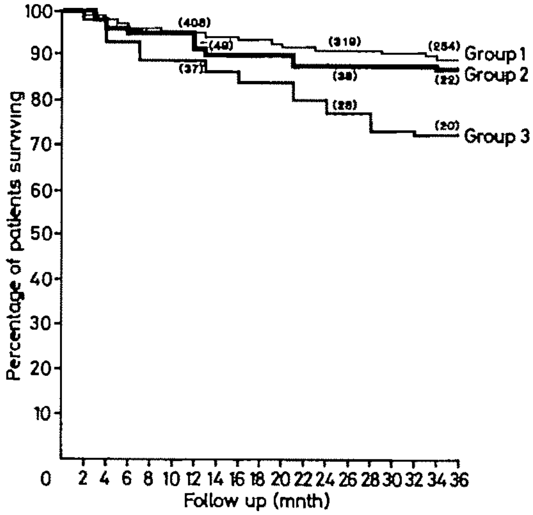

Fig 2 *Actuarial survival curve for the patients who had survived beyond 30 days after operation in each of the three groups (see legend to figure 1).*

balloon pump (table 4). Perioperative myocardial infarction was defined as the development of a new Q wave of at least 0·04 s in the postoperative electrocardiogram. This was found in 17% of operative survivors in group 2 and 15% of operative survivors in group 3. In group 1, 4% of operative survivors had evidence of perioperative myocardial infarction.

Figure 1 shows the survival curves for the three groups of patients. Patients in group 1 had a significantly better outcome than patients in group 3 ($p = 0{\cdot}001$), but not than that of patients in group 2. Of the patients with coronary artery disease, the patients who had undergone coronary artery bypass grafting (group 2) had a higher three year survival (76%) than those who did not undergo coronary artery surgery (group 3, 62%), but the difference was not statistically significant. The survival curves for the patients who had survived for more than 30 days after operation were also analysed (fig 2). Again, the outcome of patients in group 1 was better than that of patients in group 3 ($p = 0{\cdot}02$) but not than that of patients in group 2. Although patients with coronary artery disease who underwent coronary artery surgery did better than those who did not, the difference did not quite reach statistical significance. Figures 1 and 2 show that after the initial difference in early mortality, the survival curves for group 1 and group 2 are parallel. The curve for group 3, however, falls away from these two curves with time, indicating a worse long term outcome.

At the most recent follow up assessment, 86% of survivors in group 2 were in New York Heart Association class I, 8% in class II, and 6% in class III. In group 3, the proportions were 82%, 12%, and 6% respectively. There have been six late (> 30 days after operation) deaths in group 2: two of these were attributable to cardiac failure, two to malignant disease, and one each to myocardial infarction and cerebrovascular accident. In group 3, there have been nine late deaths: four caused by myocardial infarction, three by cardiac failure, and one each by cerebrovascular accident and infective endocarditis.

Discussion

Many centres perform adjunctive coronary artery grafting at the time of valve replacement in patients with combined aortic valve disease and coronary artery disease. The validity of this approach is based firstly on the principle that correction of two coexisting abnormalities should have an additive beneficial effect.[9] Secondly, although hospital mortality for aortic valve replacement tends to be higher in the presence of coronary artery disease[9 10] it is probably not affected by the additional procedure of coronary artery grafting. Bonow *et al*, however, concluded that coronary artery bypass grafting at the time of valve replacement is not advantageous as a near-routine procedure for patients with combined important aortic valve and coronary artery disease.[11]

An evaluation of the place of coronary artery grafting in patients with combined aortic valve dysfunction and coronary artery disease should be based on age and sex matched populations of patients with similar aetiology and severity of aortic valve disease, with a similar degree of coronary artery disease. The two groups of patients should be operated upon during the same period of time, and the analysis should include early and late survival, symptomatic outcome, and the incidence of late complications. But such a study has not been and perhaps never will be performed.

The advisability of routine coronary arteriography at the time of cardiac catheterisation remains controversial. Apart from defining obstructive lesions in the coronary arterial tree it is also valuable in defining anatomy of the left main stem. It has been suggested, however, that routine angiography may not be necessary in patients who do not have angina[12] and it has been proposed that valve replacement may be performed safely without this preoperative investigation.[13] Aortic stenosis was initially thought to confer some protection against the development of coronary artery disease.[14] Since the introduction of coronary angiography, the reported incidence of coronary artery disease in patients with aortic valve disease has varied between 20% and 60%.[15-17] Some have suggested that coronary artery disease is only found in patients who have angina.[18 19] Ramsdale *et al*, however, in a study of patients with valvar heart disease undergoing coronary angiography found that 13% of patients with aortic valve disease and no angina had coronary artery disease.[20] The limitations of angina in predicting the presence of coronary artery disease in patients with aortic valve disease was also found by Coleman and Soloff.[21] In the present series, 26% of patients who experienced angina had important coronary artery disease, compared with 13% of those who did not have angina. It has been shown that the unexpected finding of important coronary artery disease at the time of aortic valve replacement worsens the operative outcome.[22]

The importance of preoperative diagnosis of coronary artery disease has been suggested in studies that examine both the influence of coronary artery disease and coronary artery surgery on the morbidity and mortality of aortic valve replacement.[9 10] The present study has shown that the presence of coronary artery disease increases the risk when patients have aortic valve replacement, whether or not coronary artery bypass grafting is performed. Czer *et al* have also recently shown that coexistent coronary disease reduces early survival after aortic valve replacement.[23] In these patients, at operation and during aortic cross clamping, the heart is subject to limited distribution of either cardioplegia fluid as a protective agent or blood as an energy substrate. Although some of the patients in the present series had important coronary artery disease, they did not undergo bypass surgery. The reason for this was not usually clear; it did not seem to be related to the size of the vessel or the site of the lesion. It was probably because the value of routine myocardial revascularisation was not appreciated when the patients underwent surgery. It is also possible that patients with more widespread disease were more likely to undergo bypass surgery.

In a recent report Scott *et al* analysed the influence of several factors on operative mortality by univariate and multivariate analysis.[9] In the whole group, the presence of coronary artery disease did have an adverse influence on mortality, although the concomitant procedure of coronary artery surgery had no significant effect on operative mortality. Age was cited as an independent determinant of operative mortality in the entire group, although it was not stated whether the patients with coronary artery disease differed in age from those without coronary artery disease. Czer *et al* have recently shown that complete revascularisation does not increase operative risk when coronary artery disease is present.[23] In this series, the age difference between patients with and those without coronary artery disease was significant and may account for some of the difference in early mortality. Data supporting coronary artery disease as a risk factor are evident in reports by Loop *et al*,[2] Linhart *et al*,[24] and Cooley *et al*.[25] Nunley and co-workers considered the problems of differing characteristics of patient subgroups through relative survival computations for age and sex variation.[3] Between 1976 and 1981 they reported an operative mortality of only 5%, which is similar to that reported for isolated aortic valve replacement. Their results, together with the favourable long term outcome for the combined operation group led to the recommendation of combined aortic valve and coronary artery surgery.

Factors such as the differing severity of coronary artery disease and the variation in preoperative functional state made the comparison of different patient subgroups in the present study difficult. Although patients who received cardioplegia had a lower early mortality than those who did not, this did not explain the differences seen between the three groups. However, of the patients with coronary artery disease, those who underwent coronary artery surgery had more severe coronary disease and a worse functional state before operation than those who did not undergo myocardial revascularisation. It is noteworthy that only 11% of the early deaths in the patients with important coronary artery disease who did not undergo bypass surgery occurred in those with single vessel disease, although they formed 64% of the group. Both groups of patients with coronary artery disease had similar requirements for inotropic support after operation and similar rates of perioperative myocardial infarction. It is probable that the inotropic requirement reflects important myocardial damage more accurately than electrocardiographic changes, which do not correlate well with more sensitive indices for myocardial infarction.[26 27]

The optimal operative management of patients undergoing aortic valve replacement in the presence of coronary artery disease remains uncertain. This is important since operative mortality is almost exclusively related to myocardial infarction, which is a direct reflection of myocardial protection. It has been suggested that distal obstructions of coronary arteries should be bypassed early in the procedure to allow protection of myocardium beyond the stenoses.[26] Valve replacement and placement of distal coronary artery graft anastomoses during a single anoxic interval during cardioplegic arrest and topical hypothermia is a simpler procedure and this is associated with good results.[9 28]

In this series it is clear that the presence of coronary artery disease conferred a significant risk to surgery whether or not coronary artery grafting was performed. Furthermore, the presence of coronary artery disease that was not treated surgically had an adverse long term influence. The late deaths in patients with significant coronary artery disease who did not undergo revascularisation tended to be related to complications of coronary artery disease. This trend was seen in the report by Copeland *et al*, who also suggested that the concept of presenting a probability of survival for a large heterogeneous group of patients undergoing a procedure such as aortic valve replacement is of limited value.[10] Nunley and colleagues, however, using a more complex statistical analysis suggested that performance of coronary artery surgery returns those patients with combined aortic valve and coronary artery disease to a "prognostic class" equivalent to individuals with only aortic valve disease,[3] and supported their data by comparing survival curves with four other reported series. Revascularisation in patients with coexistent coronary artery disease seems to reduce the occurrence of late sudden death.[23] In these patients impaired preoperative left ventricular function and advanced age reduced the late survival rates.[29] The findings of the present study suggest that myocardial revascularisation returns patients with aortic valve and coronary artery disease to a prognostic "curve" similar to that of patients with isolated aortic valve disease.

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When does the risk of acute coronary heart disease in ex-smokers fall to that in non-smokers? A retrospective study of patients admitted to hospital with a first episode of myocardial infarction or unstable angina

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SUMMARY Nine hundred and seventy eight patients admitted with a first myocardial infarction or episode of unstable angina were studied to determine for how long after they gave up smoking did the risk in ex-smokers continue to resemble those of current smokers. Logistic regression was used to calculate a score, based on a combination of age, cholesterol, and hypertension, that separated current smokers from lifetime non-smokers. When this function was applied to ex-smokers, only those who had given up at least 15 years before the attack had a risk factor profile similar to that of non-smokers. Those who had given up less than five years before the ischaemic attack had a significantly higher level of other risk factors than current smokers; those who had stopped for between five and 15 years had levels similar to those of current smokers.

Ex-smokers are at higher risk of acute coronary disease for at least 15 years after stopping, but some immediate reduction in risk is possible.

Cook *et al* reported that former smokers may be at a significantly greater risk of developing acute coronary heart disease for up to 20 years after giving up smoking than people who have never smoked.[1] Earlier studies had suggested that the risk diminished more rapidly after stopping,[2-8] with ex-smokers showing a significant[2-5] or almost complete[6-8] reduction in risk in as little as two years after giving up.

Most data on the effect of stopping smoking on subsequent risk have been drawn from prospective population studies, but the low incidence of acute episodes and the small numbers of ex-smokers may mean that all but the largest prospective studies lack the statistical power to detect modest differences in risk between ex-smokers and non-smokers (that is those who have never smoked).

Studies of patients experiencing a first acute episode of coronary heart disease can be used to clarify the role of individual risk factors.[9] If we regard this episode as marking a definable level of the progress of coronary heart disease, we would expect current smokers to have lower levels of other risk factors—cholesterol, hypertension, and age—than patients who have never smoked. The risk factor "profile" that discriminated best between current and non-smokers could be applied to ex-smokers. If it differed from that found in non-smokers, the ex-smokers must have had an acute episode of coronary heart disease despite a lower level of the risk factors of cholesterol, hypertension, and age. Such a result implies a continued risk derived from their previous smoking.

We used multiple logistic regression analysis to estimate the length of time after the end of smoking for which ex-smokers are at a significantly greater risk of developing acute coronary heart disease than those who have never smoked.

Patients and methods

From January 1980 to April 1985 inclusive, all patients admitted to the coronary care unit of St

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Vincent's Hospital with a first episode of unstable angina or myocardial infarction were included in a computerised register.

Myocardial infarction was diagnosed when there was typical cardiac pain at rest with abnormal Q waves in the electrocardiogram or a twofold or greater rise in serially measured cardiac enzymes (serum glutamic oxaloacetic acid transaminase, creatine kinase, and lactate dehydrogenase). Unstable angina was diagnosed when there was cardiac pain at rest with serial ST and T wave changes in the electrocardiogram but with normal or a less than twofold increase of cardiac enzymes.

Patients were classified as non-smokers if they had never regularly smoked as many as one cigarette a day, ex-smokers if they had smoked less than one cigarette a day for at least three months before admission, and current smokers if they had regularly smoked at least one cigarette a day in the three months before admission. Pipe and cigar smoking were noted, as was the age at which ex-smokers had stopped. Current and former pipe or cigar smokers were classified as current or ex-smokers in the same way as cigarette smokers. Patients had to have stopped for three months to be classified as an ex-smoker. Total serum cholesterol and high density lipoprotein fraction were assayed in blood samples taken, in most cases, within 12 hours of onset of acute symptoms.

Patients were categorised as hypertensive (*a*) if the mean of all blood pressure measurements taken on the fourth day after admission was ⩾90 mm Hg; (*b*) if the patient was known to have been treated for hypertension before admission; (*c*) if at least two of the following three criteria were present:

(1) past history of hypertension detected by a physician (whether or not it was treated),

(2) electrocardiographic evidence of left ventricular hypertrophy,

(3) hypertensive retinopathy.

A multiple logistic regression was calculated to find the best combination of age, cholesterol, and hypertension to discriminate between current smokers and non-smokers. Scores on the function were then computed for ex-smokers as well as for current smokers and non-smokers. Ex-smokers were classified in five year groups, according to the length of time since they had given up. We compared mean function scores between groups by Tukey's procedure to correct for errors arising from repeated comparison of means.[10]

Results

Nine hundred and eighty seven patients were admitted to the study. Ten of these had to be excluded from the analysis because we could not record their smoking habits. There were 639 men (65·4%) and 338 women (34·6%). Two hundred and four patients (20·9%) were admitted with unstable angina and 773 (79·1%) with myocardial infarction, of whom 49·7% had a complicated in-hospital course. There were 515 current smokers, 264 ex-smokers, and 198 non-smokers. Because many data were missing we examined the relation between missing data and smoking state (table 1). Hypertension could not be assessed in 28 cases, age had not been recorded in 7, and serum cholesterol had not been measured in 201.

Table 2 shows the relation between lifetime smoking habits and risk factors. When patients were examined in three groups—non-smokers, ex-smokers, and current smokers—there were significant differences in the distributions of age, cholesterol, and hypertension. The significance values for these differences are shown below table 2. When individual groups were compared, all three groups differed significantly (p < 0·05) from one another in age and the proportion with hypertension. The mean serum concentration of cholesterol was significantly different in non-smokers (6·51 mmol/l) and ex-smokers (6·10 mmol/l), but the concentration in current smokers (6·25 mmol/l) did not differ significantly from either.

A direct logistic regression analysis performed on current and non-smokers yielded significant independent predictive associations between smoking and both age and hypertension (both p < 0·0001). Although cholesterol was not significantly independently associated with smoking after allowance for age and hypertension (p = 0·068), it was retained in the model in view of its borderline probability. The resulting function, then, is a combination of age, cholesterol, and hypertension calculated so as to place smokers at one end of a range of risk and non-smokers at the other. We refer to it, for simplicity, as a discrimination score. To examine the

Table 1 *Distribution of missing data in the study group (number of valid cases, followed by number of missing cases in parentheses)*

Smoking state	*Cholesterol*	*Age*	*Hypertension*	*All three variables*
Current smokers	431 (84)	512 (3)	501 (14)	424 (91)
Ex-smokers	197 (67)	264 (0)	257 (7)	196 (68)
For <5 yr	67 (26)	93 (0)	91 (2)	67 (26)
For 6–10 yr	42 (15)	57 (0)	56 (1)	41 (16)
For 11–15 yr	28 (7)	35 (0)	34 (1)	28 (7)
For 16–20 yr	34 (8)	42 (0)	42 (0)	34 (8)
For >20 yr	26 (11)	37 (0)	34 (3)	26 (11)
Never smoked	148 (50)	194 (4)	197 (1)	145 (53)

Data on length of time since the patient stopped smoking were missing in 10 of 264 cases.

Table 2 *Risk factors in current smokers, non-smokers, and ex-smokers*

Category	*Cholesterol (mean (SE)) (mmol/l)*	*Percentage hypertensive (SE)*	*Age (yr) (mean (SE))*	*Discrimination* score (SE)*
Current smokers	6·3 (0·07)	25% (2·0)	59 (0·5)	1 00 (0·009)
Ex-smokers	6 1 (0 09)	36% (3·2)	63 (0 7)	0·91 (0 015)
For <5 yr	6·1 (0·22	38% (6 4)	60 (1 5)	0·90 (0 028)
For 6–10 yr	6 0 (0·16)	27% (6·4)	61 (1·5)	0·98 (0·030)
For 11–15 yr	6·0 (0 23)	35% (8·6)	60 (1 6)	0·96 (0·042)
For 16–20 yr	6 2 (0 24)	43% (8 0)	64 (1·6)	0·89 (0 037)
For >20 yr	6 1 (0·26)	38% (8 7)	69 (1·2)	0·81 (0 033)
Never smoked	6·5 (0·13)	51% (3·6)	66 (0 8)	0·80 (0 020)
	F = 3 56	χ^2 = 49 38	F = 47 98	F = 68 4
	p = 0·029	p < 0 001	p < 0 001	p < 0 001

*Based on age, cholesterol, and hypertension (see text)
Cholesterol: 1 mmol/l = 38·6 mg/dl.
Statistics are for three way classification of smokers (non, ex, and current)
For comparison of pairs of means, see text.

position of ex-smokers on this range we calculated their scores according to this function. Table 2 shows the mean function score for current smokers, ex-smokers, and non-smokers. All three groups differed significantly from one another at an alpha level of 0·05.

In order to determine how long after they stop smoking ex-smokers continue to have a significantly higher risk than non-smokers, we divided ex-smokers into groups based on the interval since they stopped, divided up into five year periods. Table 2 shows that the risk factor score based on the logistic regression declined with length of time since smoking was stopped. However, only those patients who had given up at least 15 years before their first episode of acute coronary heart disease had a mean risk score that did not differ significantly (p > 0·05) from the mean risk score of a non-smoker.

Discussion

Smoking is a major risk factor for acute coronary heart disease. Furthermore, it is widely accepted that those who stop smoking reduce their risk. The most optimistic view is that risk declines rapidly after the end of smoking and soon resembles that of non-smokers.[2 8] This implies that the role of smoking as a risk factor in coronary heart disease is not primarily atherogenic, a view which has received some support from angiographic investigations.[11] A recent report from the British Regional Heart Study, on the other hand, found no evidence of a rapid decline in risk,[1] and other studies have shown a continuing excess risk lasting for up to twenty years.[3 4]

Several of the studies showing no lasting effect of smoking on risk of acute coronary heart disease were hampered by small event rates.[6 8] Furthermore, the endpoints studied ranged from fatal coronary disease through non-fatal infarction to any manifestation of acute coronary ischaemia, as in the case of the present study. So, despite a considerable body of research the two central questions remain unanswered: is there a drop in risk immediately after the end of smoking and for how long does a residual additional risk remain? We attempted to cast light on these questions by making use of hospital data. The technique used does not allow an estimate of the absolute level of risk because there is no denominator population and inevitably the data are incomplete. Nevertheless, it is based on a large series of coronary events which were scarce in prospective studies of populations.

The method we used assumed that non-smokers who developed coronary heart disease did so because of higher levels of other risk factors—age, hypertension, and/or cholesterol. Accordingly, if an acute episode of coronary heart disease develops in ex-smokers with a lower loading of other risk factors than non-smokers, the ex-smokers must have a residual risk associated with smoking which acts on their advanced coronary artery disease to precipitate a first acute coronary event.

Ex-smokers who had given up recently tended to be younger than ex-smokers who had given up for longer. One explanation for this is that older ex-smokers were more likely to have given up for longer simply because they were older. Two factors, however, argue against this interpretation: the first is that the increase in age from current smokers through ex-smokers to non-smokers is consistent with the hypothesis that the lower the person's exposure to smoking, the slower the progression of atherosclerosis. Secondly, our findings accord with those of Cook *et al* who reported no immediate decline in cardiovascular risk when smoking stopped, and a continuing risk persisting for up to 20 years.[1] Further analysis showed a dose response relation between the number of years of smoking and subsequent risk. Since we had no information on the age at which our patients started smoking we could not analyse our data in this way. A recent report on smoking, clotting factors, and coronary heart disease risk by the Northwick Park Heart Study found that it took five years of non-smoking for clotting factors in ex-smokers to fall to values in non-smokers.[12] In ex-smokers there was a relation between total years smoking and concentrations of clotting factor. These findings may in part explain both the results presented here and those of the British Regional Heart Study.[1] We can offer no explanation for the difference between the effect of stopping smoking on coronary risk in the general population, which seems to be gradual and small, and the immediate halving of the risk that we reported in patients who gave up smoking after an episode of acute coronary heart disease.[13] Such patients seem to be more susceptible to the effects of smoking than the general population, but no mechanism for this increased susceptibility has yet been established.

Serum concentrations of cholesterol were lowest in ex-smokers in our patient group, intermediate in current smokers, and highest in non-smokers. It is likely that ex-smokers make other lifestyle changes aimed at risk reduction and these reduce their cholesterol concentrations to below values in their smoking counterparts. The role of such lifestyle changes as a possible confounding factor in the association between giving up smoking and subsequent coronary risk should be studied.

The mode of action of smoking in the causation of coronary heart disease is still unproven. It is likely, indeed, that it acts in two ways. First, smoking may increase the rate of atherosclerosis for any given serum concentration of cholesterol, thus bringing forward the age at which atherosclerosis will be sufficiently advanced to lead to an acute ischaemic event. Secondly, smoking may exert vasospastic and thrombogenic effects, thus precipitating an acute coronary event when the degree of atherosclerosis is less than would be required for a coronary event in a non-smoker. The rapid decline in risk found by some studies may reflect the removal of the effect of smoking in precipitating an infarction, while the continuing risk reported by others presumably reflects a continuing atherogenic effect of previous smoking. Our data provide support for this latter effect, indicating that although there is a suggestion of a lowering of risk immediately after the end of smoking, the risk factor levels found in ex-smokers are not distinguishable from those in current smokers until 15 years after they stop smoking; this suggests a continuing smoking associated risk in this period. So, although it is never too late to give up smoking nor is it ever too early.

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Assessing cardiac pumping capability by exercise testing and inotropic stimulation

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SUMMARY In heart failure both functional capacity and prognosis are primarily determined by the degree of pump dysfunction. Although data on haemodynamic function at rest may indicate impaired cardiac function, they do not assess the capacity of the heart to respond to stress. Maximal bicycle ergometry and incremental intravenous inotropic stimulation in 31 patients with moderately severe heart failure were evaluated as methods of stressing the heart to determine cardiac pumping capability, which is defined as the cardiac power obtained during maximal stimulation. There was good agreement between the cardiac pumping capabilities assessed by these two methods. Maximal cardiac power output was better than maximal cardiac output and left ventricular stroke work index in representing cardiac pumping capability, because it was less dependent on the type of stimulation used during evaluation.

Inotropic challenge is at least as effective as exercise testing in assessing cardiac pumping capability in heart failure, and may be a better method in patients who find physical exercise difficult.

The primary defect in heart failure is the inability of the cardiac pump to deliver sufficient hydraulic energy to maintain the circulation required by the metabolism during exercise and, when failure becomes more severe, at rest as well.[1] Variables such as left ventricular ejection fraction, cardiac index, and left ventricular stroke work index are often measured to assess the extent of the primary defect.[2 3] Unfortunately, these variables correlated poorly with exercise capacity[4 5] and prognosis in individual patients with heart failure.[1 6]

An alternative method of evaluating cardiac impairment has been proposed.[7] It was suggested that cardiac power output is, from the point of view of fluid dynamics, the most logical variable to represent cardiac performance. Whether it reflects cardiac function more closely than the more commonly used variables, such as cardiac index and left ventricular stroke work index, remains to be seen. In theory, how good the heart is as a pump can be best represented by the maximum hydraulic power output achieved by the heart during maximal stimulation, and this value is termed the cardiac pumping capability.[7] This variable, when determined by maximal inotropic stimulation, has been shown to be an accurate predictor of the prognosis of individual patients with severe pump failure.[1] Because it is not known whether this pharmacologically determined cardiac pumping capability bears any relation to the functional capacity of the impaired heart during exercise, we compared cardiac pumping capability measured during incremental dobutamine infusion with that measured during symptom limited exercise.

Patients and methods

PATIENTS

We studied 31 patients (24 men and seven women) in moderate to severe heart failure in sinus rhythm (mean age of 59 years (range 44–69 years)). All except two patients (class IV) had symptoms in New York Heart Association class III. Dyspnoea on exertion was the predominant symptom in all patients, although two patients felt that fatigue was equally limiting. Patients with exercise induced angina or important ventricular arrhythmias were excluded. The mean (SD) left ventricular ejection fraction was 27·2 (11·5)%. Two patients had dilated cardiomyopathy and the remainder had heart failure secondary to coronary artery disease. All the patients had had heart failure for more than four months before

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evaluation and none had a myocardial infarction in the six months before study. All patients gave informed consent to the study, which was approved by the ethical subcommittee of the East Birmingham Hospital.

EXPERIMENTAL PROTOCOL

An electrocardiograph, thermodilution Swan-Ganz catheters, and arterial cannulas were used to measure heart rate, right atrial pressure, pulmonary arterial and pulmonary wedge pressures, systemic arterial pressure, and cardiac output, which was measured in triplicate. Baseline resting haemodynamic data were measured every 20 minutes until the consecutive data did not vary by more than 10%. Haemodynamic data were also collected during exercise. Patients exercised in a semierect position (at 45–60° to the horizontal) on a bicycle ergometer, starting at 10–25 W and increasing in steps of 10–25 W every three minutes. The workloads were selected so that the patients reached peak exercise in less than 10 minutes. The exercises were terminated by exhaustion, dyspnoea, or leg muscle fatigue, or by important ventricular arrhythmia. None of these patients had to stop exercising because of arrhythmia. The exercise tests were performed in the postabsorptive state at about the same time of day, and four hours after the ingestion of diuretics. After patients had rested for four hours, we gave increasing doses of dobutamine starting at 2·5 μg/kg/min and increasing by 2·5 or 5·0 μg/kg/min every 5–10 minutes to a maximum of 15–30 μg/kg/min. The maximum dose was reached when there was no further increase in cardiac output and cardiac power output, or when a symptom became intolerable or important arrhythmia developed. One patient asked for the dobutamine infusion to be stopped (at a rate of 15 μg/kg/min) when considerable vasodilatation caused a sensation of intolerable hotness. In two patients the infusion (> 10 μg/kg/min) was stopped because of ventricular bigeminy that prevented further increases in cardiac power output.

CALCULATIONS

From the haemodynamic data obtained, where all pressures were expressed as mm Hg, cardiac index (CI), left ventricular stroke work index (LVSWI), pulmonary vascular resistance (PVR), systemic vascular resistance (SVR), and cardiac power output (CPO) were calculated as follows: CI (l.min^{-1}.m^{-2}) = cardiac output/body surface area; LVSWI (g.m.m^{-2}) = (mean systemic arterial pressure − mean pulmonary wedge pressure) × CI × 0·136/heart rate; PVR (dyn.s.cm^{-5}) = (mean pulmonary arterial pressure − mean pulmonary wedge pressure) × 80/cardiac output; SVR (dyn.s.cm^{-5}) = (mean systemic arterial pressure − mean right atrial pressure) × 80/cardiac output; CPO (W) = (mean systemic arterial pressure − mean right atrial pressure) × cardiac output × 2·2167 × 10^{-3}.

The maximum cardiac power output during exercise testing (CPO_E) was that obtained when the patient was performing at maximal exercise workload. The maximum cardiac power output during dobutamine infusion (CPO_D) was determined by the highest cardiac power output value obtained during the incremental dobutamine stimulation.

Statistical analysis was by Student's paired *t* test. Differences were taken to be significant at $p < 0·05$. Results are expressed as mean (1 SD). We used the statistical method of Bland and Altman[8] to assess the agreement between the two methods of evaluating cardiac pumping capability (dobutamine and exercise challenge).

Table *Haemodynamic effects of peak exercise and dobutamine infusion (mean (SD))*

Variable	*Control*		*Dobutamine*		*Control*		*Exercise*	
Heart rate/min	75·9	(12·3)	109·4	(17·6)	78·6	(12·6)	104·6	(16·9)
Mean right atrial pressure (mm Hg)	7·4	(5·8)	5·1	(4·4)	7·6	(5·7)	10·9	(7·7)**
Mean pulmonary arterial pressure (mm Hg)	27·7	(12·4)	26·9	(12·4)	27·1	(12·3)	37·8	(15·7)**
Mean pulmonary artery wedge pressure (mm Hg)	16·0	(9·2)	11·4	(7·3)	15·5	(9·0)	19·9	(10·3)**
Mean systemic arterial pressure (mm Hg)	89·5	(13·8)	88·7	(13·1)	91·2	(12·3)	102·7	(15·6)**
Cardiac index (l.min^{-1}.m^{-2})	2·45	(0·71)	4·32	(1·03)	2·44	(0·73)	3·76	(1·10)*
Cardiac power output (W)	0·83	(0·31)	1·41	(0·42)	0·82	(0·31)	1·38	(0·49)
Pulmonary vascular resistance (dyn.s cm^{-5})	236	(160)	174	(126)	238	(179)	231	(171)
Systemic vascular resistance (dyn.s.cm^{-5})	1600	(426)	918	(286)	1626	(428)	1163	(318)
Left ventricular stroke work index (g m.m^{-2})	34·1	(13·8)	43·2	(14·4)	34·2	(14·7)	42·6	(18·5)

*$p < 0·05$ and **$p < 0·01$ for dobutamine *v* exercise.

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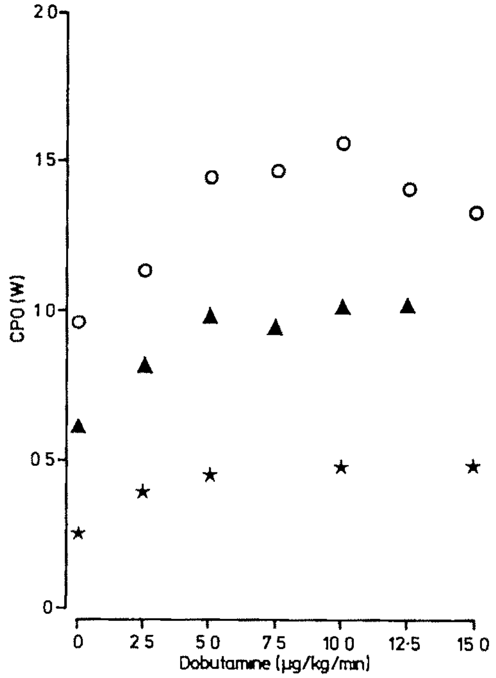

Fig 1 *Cardiac power output (CPO) during incremental dobutamine infusion in three representative patients.*

Results

The table compares the haemodynamic effects of dobutamine challenge and exercise. Both dobutamine and exercise increased heart rate, cardiac index, cardiac power output, and left ventricular stroke work index, and the peak values of these variables (except cardiac index) produced by both types of stimulation were not significantly different. Right and left ventricular filling pressures were reduced by dobutamine, but increased by exercise. Although dobutamine tended to reduce pulmonary and systemic vascular resistance more than exercise, resulting in lower pulmonary and systemic arterial pressures and higher cardiac output, similar left ventricular stroke work index and cardiac power output were obtained during both stresses.

Figure 1 shows cardiac power output during incremental dobutamine infusion in three representative patients. The increases in cardiac power output were more prominent at the lower doses of dobutamine, from 0 to 7·5 µg/kg/min. Above 10 µg/kg/min the increases in cardiac power output with increments of dobutamine tended to reach a plateau. These patients had not been exposed to dobutamine and had not developed tolerance to it. When tolerance developed (for example after more than 24 hours of dobutamine infusion at >10 µg/kg/min),

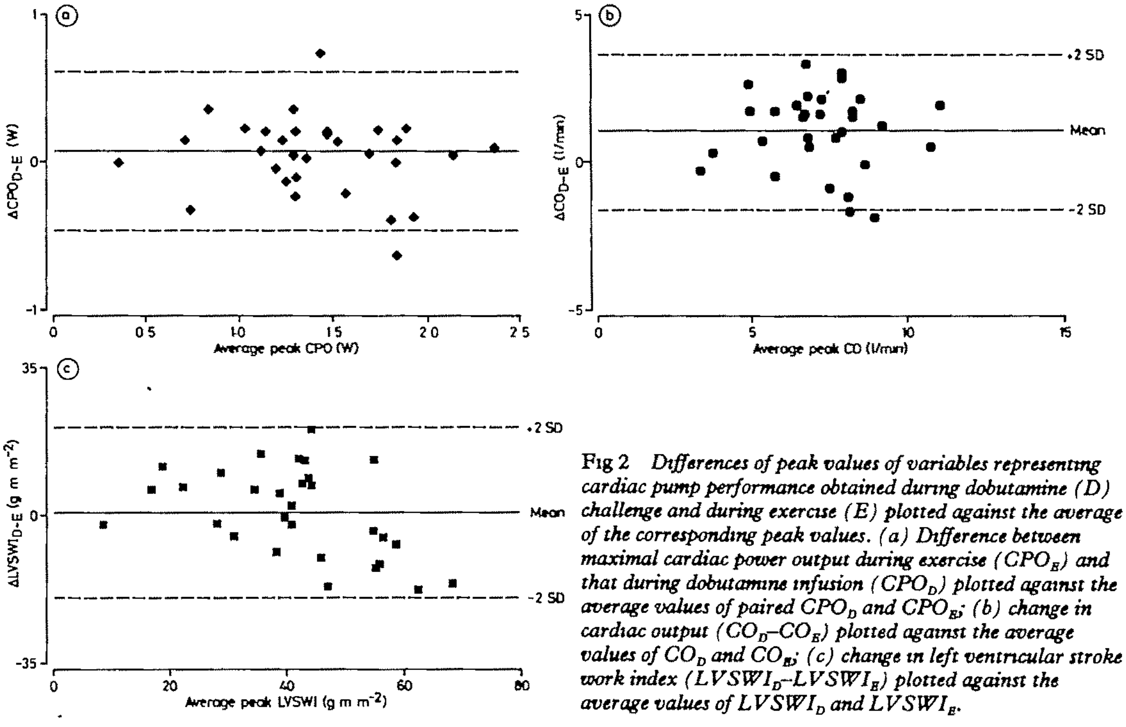

Fig 2 *Differences of peak values of variables representing cardiac pump performance obtained during dobutamine (D) challenge and during exercise (E) plotted against the average of the corresponding peak values. (a) Difference between maximal cardiac power output during exercise (CPO_E) and that during dobutamine infusion (CPO_D) plotted against the average values of paired CPO_D and CPO_E; (b) change in cardiac output (CO_D–CO_E) plotted against the average values of CO_D and CO_E; (c) change in left ventricular stroke work index ($LVSWI_D$–$LVSWI_E$) plotted against the average values of $LVSWI_D$ and $LVSWI_E$.*

higher doses of dobutamine (for example > 20 μg/kg/min) were required to attain the peak cardiac power output. CPO$_D$ was unambiguously identified for each patient because values either reached a plateau at high doses or showed a peak followed by a decline.

The statistical method of Bland and Altman[8] showed good agreement between the cardiac pumping capability as evaluated by measuring peak cardiac performance (represented by peak cardiac power output) during maximal dobutamine challenge and maximal exercise (fig 2a). When cardiac output was used to represent cardiac performance (fig 2b) the scatter of the points around the mean was similar, with the coefficient of variation of the differences (SD of differences/mean of the average peak values) being 0·19 in both assessments. However, the mean difference between CPO$_D$ and CPO$_E$ was closer to zero than that between CO$_D$ and CO$_E$. There were more points above than below zero in fig 2b. In other words, the peak cardiac output measured during dobutamine challenge tended to be greater than that measured during exercise. In fig 2c the differences between left ventricular stroke work index measured by the two methods were plotted against the corresponding average left ventricular stroke work index. Like fig 2a, the mean value of the differences was close to zero. However, the scatter of the points about the mean in fig 2c (coefficient of variation $= 0{\cdot}24$) was greater than those in figs 2a and b (coefficient of variation $= 0{\cdot}19$).

Discussion

EVALUATION AT REST *v* DURING EXERCISE

The heart of a patient in cardiac failure has limited functional capacity. Measurement of cardiac performance at basal resting states is helpful in detecting the presence of cardiac impairment (for example the low left ventricular ejection fraction of 27 (12)% and cardiac index of 2·5 (0·7) l/min/m^2 in these patients), but it often fails to differentiate the degree of functional cardiac failure.[4 5] A patient's functional ability should not be assessed from haemodynamic measurements made only at rest.

To determine how well a heart functions as a pump during stress its response to maximal stimulation must be assessed. Clinically, the most important form of stimulation is physical exercise. At rest the cardiac power output of a normal subject is approximately 1 W, and at maximal exercise it is approximately 6 W.[7] The average (SD) cardiac power output of patients in this study was 0·8 (0·3) W at rest and 1·4 (0·5) W during maximal exercise, indicating a considerable reduction in cardiac pumping capability. Thus haemodynamic measurement during stress gives a clearer indication of failing cardiac function than haemodynamic evaluation at rest.

CARDIAC PERFORMANCE EVALUATED BY CARDIAC POWER OUTPUT, CARDIAC OUTPUT, AND LEFT VENTRICULAR STROKE WORK INDEX

The data shown in figs 2a and b suggest that cardiac power output is a better variable to represent cardiac pumping capability than cardiac output. For similar degree of cardiac stimulation, cardiac pumping capability during dobutamine challenge tended to be overestimated if cardiac output were used as the indicator of cardiac performance. This was because at peak stimulation blood pressure was significantly lower with dobutamine challenge than with exercise (table). There was a tendency for dobutamine to produce greater systemic arterial vasodilatation than exercise. Any drug that causes appreciable vasodilatation is liable to exaggerate cardiac output because the heart's capacity for generating pressure is converted into a capacity for generating flow.

Like cardiac power output, left ventricular stroke work index accounts for the capacity of the heart to generate both pressure and flow. So we were not surprised to find that the scatters of the differences above and below zero in fig 2c were almost equal. Left ventricular stroke work index is energy output per stroke whereas cardiac power output is energy output per unit time. Thus unlike cardiac power output, left ventricular stroke work index does not contain the factor heart rate. When heart rate is held constant these two measures of cardiac pumping capacity are equal. As far as maintaining the circulation is concerned, it does not matter how much hydraulic energy per stroke the heart delivers into the circulation, as long as the total delivered per unit time is sufficient to replenish the energy lost in the vasculature, and able to maintain organ perfusion and metabolism in tissues. Thus for any two hearts with the same limitation in generating stroke work, the one that is capable of a greater increase in heart rate would be able to impart more hydraulic energy into the vasculature and thus maintain a higher level of circulation and metabolism. Hence from the theoretical point of view, cardiac power output would be expected to be a better functional representation of cardiac pumping capability than left ventricular stroke work index. In patients with ischaemic cardiac failure, it is not uncommon to see excessive or inadequate chronotropic responses to exercise. The greater scatter of the points in fig 2c than in fig 2a suggests that the chronotropic responses of the hearts to dobutamine and exercise were different. Also, in fig 2c, peak left ventricular stroke work index was apparently higher with dobutamine challenge than with exercise when values were < 35 g.m.m^{-2} but the converse was true for higher values (> 50 g.m.m^{-2}). This implies that the use of left ventricular stroke work index as a measure of cardiac pumping capability depends on the mode of stimulation used and whether such stimulation can induce an appropriate chronotropic response.

PHARMACOLOGICAL AGENTS TO STIMULATE THE HEART

Dobutamine was chosen as the stimulating agent primarily because it was the most commonly used intravenous positive inotropic agent in the treatment of heart failure in our coronary care unit. As an adrenergic agonist it resembles the activity of endogenous catecholamines.[9 10] One concern is that, as there is appreciable β adrenoceptor down regulation in severe heart failure,[11] adrenergic agonists may not be the ideal agent to use. The combined use of dobutamine with a phosphodiesterase inhibitor[12] may circumvent this problem, but the combined arrhythmogenic effects of these drugs have not been ascertained. Furthermore, it may be argued that when patients exercise they have to rely on the cardiac response to adrenergic drive to augment their cardiac performance. Hence, from the functional point of view, the amount of cardiac reserve available via adrenergic stimulation is that which is of clinical and functional relevance.

A COMPARISON OF PHARMACOLOGICAL AND PHYSIOLOGICAL STIMULATION

This study showed that cardiac pumping capability measured during dobutamine challenge correlated well with that measured during symptom limited bicycle exercise testing, but there are advantages and disadvantages with both methods. The disadvantage of exercise testing lies in the difficulty in determining the true maximum exercise. It has been proposed that one way of identifying this point is to use the plateau of oxygen consumption as maximum exercise is approached,[13 14] but this proposal has been challenged.[15] In contrast, CPO_D can be easily identified during incremental dobutamine infusion (fig 1). Furthermore, since CPO_D can be unambiguously determined (fig 1), it would be reasonable to propose that a *necessary* (but not *sufficient*) condition which must be satisfied before it can be claimed that the point of maximum exercise has been reached, is the attainment of CPO_E that is greater than CPO_D.

Different exercise protocols may stress the heart differently, for example, more rapid increases in workload lead to earlier attainment of the maximum workload and a greater value of CPO_E.[7 16] During incremental dobutamine infusion, however, the ventricular filling pressures tend to decrease, which implies that CPO_D might have been higher had it been possible to increase the preload concomitantly. Both exercise and incremental dobutamine infusion are potentially arrhythmogenic, and the occurrence of frequent ventricular extrasystoles or tachycardia tends to limit the maximal cardiac power output obtained.

Dobutamine challenge may be the best method of assessing cardiac pumping capacity particularly when the patient is unable or unwilling to undergo maximal exercise testing. Invasive techniques are not always needed because non-invasive techniques of measuring cardiac output are now available (for example Doppler echocardiography).[17]

METHODS OF DETERMING PROGNOSIS

Direct and indirect indicators of cardiac function have been used as prognostic indices in heart failure. Most of the direct indicators of cardiac function have been shown to give some measure of the prognosis in different patient groups,[18 19] but the considerable overlap of values between survivors and non-survivors limited the usefulness of these variables as discriminators in individual patients.[1 6] Unfortunately, cardiac function was evaluated at basal resting states in these studies. An indirect measure of cardiac function that uses peak oxygen uptake during maximal exercise was shown to be a good prognostic index.[20] The reason for this is that peak oxygen uptake is obtained during maximal stress. In other words, it is an indirect measure of the cardiac pumping capacity. However, it is also dependent on other factors as well, notably the regional distribution of blood flow and the way that exercising skeletal muscle consumes oxygen, and these factors are not known to influence prognosis unless the peripheral tissues become ischaemic at rest in terminal heart failure. Hence, a more direct measure of cardiac pumping capacity would be expected to be a better indicator of prognosis.[1]

The serum concentration of noradrenaline is also an indirect marker of cardiac dysfunction, and it has also been shown to be quite a good indicator of prognosis.[21 22] The higher the noradrenaline concentration in severe heart failure the more likely is downregulation of the β adrenoceptors.[11] The evaluation of cardiac responsiveness to adrenergic stimulation (for example, dobutamine infusion) combines the information on cardiac pumping capacity and the sympathetic neurohormonal state of a patient with heart failure.[1] It is therefore not surprising that this method of assessing prognosis is much more accurate than other methods of determining prognosis. What was not clear from the previous study was whether cardiac pumping capacity determined by dobutamine challenge is related to functional cardiac pumping capacity. This study showed a good agreement between the pharmacologically determined cardiac pumping capacity and physiologically determined cardiac pumping capacity. We can infer from this that the cardiac pumping capacity assessed by dobutamine challenge is a true indication of the functional capacity of the impaired heart during exercise. We therefore recommend that whenever a patient requires inotropic support, an incremental infusion of dobutamine should be given because the measurement of cardiac pumping capacity obtained will give important information on prognosis, which will help in deciding the future management of the patient.

The concept of evaluating cardiac function by cardiac pumping capacity is new. Its clinical utility is based on the understanding that measurement of cardiac function in the basal unstressed states is uncertain because of the variable degrees of activation of neurohormonal compensatory mechanisms on the one hand and on the other the variable states of somnolence or excitation of the patient during measurement. To avoid ambiguity, evaluation must be performed at maximal stress. The results of this study suggest that pharmacological stress is as good as physiological stress. The variable chosen to represent cardiac performance at this maximal point must not only reflect some isolated aspects of cardiac function (for example myocardial contractility) but also the overall integrity of the cardiac pumping. We found that cardiac power output was a better indicator of overall cardiac performances than cardiac index and left ventricular stroke work index.

We thank Mrs Elsie Gale and her team of technicians who helped to perform this study.

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Lack of correlation between intracavitary thrombosis detected by cross sectional echocardiography and systemic emboli in patients with dilated cardiomyopathy

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SUMMARY The correlation between intracavitary thrombosis detected by cross sectional echocardiography and systemic embolism was studied in 126 consecutive patients with idiopathic dilated cardiomyopathy who were examined from January 1980 to September 1987. A total of 1041 serial echocardiograms were obtained with 3·5 and 5 MHz transducers. The mean follow up period was 41·2 months. The survival rate was 88% at two years and 56% at five years. Echocardiography showed intracavitary thrombi in 14 (11·1%) patients; 13 were mural and 11 were localised at the apex of the left ventricle. Twelve patients (8·4%) had systemic emboli; this corresponded to an incidence of new embolic events of 1·4 for 100 patient-years. Patients with intracavitary thrombi or systemic emboli were treated with oral anticoagulants, as were nine in functional class IV of the New York Heart Association, for 61 patient-years. The cumulative observation period for the whole population study was 418 patient-years. None of the patients with intracavitary thrombosis had embolic complications and none of those with embolism had intracavitary thrombi. Rates of intracavitary thrombosis and systemic embolism in this series were low and there was no overlap between the two events. This may have been because the patients did not have severe dilated cardiomyopathy, because echocardiography did not detect all the thrombi, or because patients were treated with oral anticoagulants.

The presence of intracardiac thrombosis detected by cross sectional echocardiography is not predictive of systemic embolism in patients with idiopathic dilated cardiomyopathy. Criteria for the use of the anticoagulant treatment remain largely empirical in these cases.

Although intracardiac thromboses have been identified by cross sectional echocardiography in a high percentage of patients with dilated cardiomyopathy,[1] the correlation of these findings with clinical evidence of systemic embolism is still controversial.[2] Because this may be relevant to indications for anticoagulant treatment in these patients, we studied a series of patients with dilated cardiomyopathy by serial cross sectional echocardiography to see whether intracardiac thrombosis was correlated with embolic complications.

Patients and methods

One hundred and twenty six patients with dilated cardiomyopathy aged 19–72 years (mean 54), 31 women and 95 men were studied at our hospital from January 1980 to September 1987. All patients had a history of cardiac failure. Patients with systemic hypertension (> 160/90 mm Hg), diabetes, congenital, valvar, and ischaemic heart disease were excluded by clinical history and a physical and laboratory examination. Left ventriculography and coronary angiography were performed in 62 patients. Echocardiographic criteria for the diagnosis of

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dilated cardiomyopathy were an enlarged cardiac left ventricular diastolic dimension (normalised for body surface area), decreased mitral valve opening, and fractional shortening of the left ventricle <25%. Normal values were derived from published data by Feigenbaum.[3] Angiographic criteria were the absence of critical obstructions (≥50%) of the right coronary artery, anterior descending and circumflex branches of the left coronary artery and an ejection fraction of ≤0·45.

M mode and cross sectional echocardiography were performed at the initial evaluation in the study and every six months thereafter. When intracoronary thrombosis was identified or an embolic event occurred echocardiograms were performed within the next month and then every three months. A total of 1041 echocardiograms were performed. The follow up period lasted 1–92 months (mean 41·2). The survival rate was 88% at two years and 56% at five years. Echocardiograms were performed with a Smith Kline instrument (model 5000) and a 3·5 MHz transducer. When a left ventricular thrombus was detected the examination was repeated with a 5 MHz probe. Echoes were recorded on a Panasonic video recorder (model 8500). Echocardiographic studies were performed in the parasternal and apical views with the patient in the supine position or the 30°–45° left lateral position. Two chamber and four chamber views gave a better image of the left ventricle, particularly the apex. Left ventricle thrombosis was diagnosed when we saw abnormal intracavitary echoes that resembled a mass adjacent to the ventricular wall and clearly were distinguishable from papillary muscle, trabeculae, and endocardium. These were generally found near the cardiac apex, protruding into the cavity. They were fixed or occasionally mobile. The echoes were unlike those coming from the adjacent myocardium.[4] The echocardiographic studies were reviewed independently by two experienced echocardiographers and reproducibility was 100%.

Systemic embolisation was diagnosed when a patient had a stroke, transient ischaemic cerebral attacks, acute vascular occlusion in the legs, or sudden renal pain with haematuria. In all patients the diagnosis was confirmed either by scintiscan, computed axial tomography, or selective arteriography.

One hundred and twelve patients had ambulatory electrocardiographic monitoring (Holter technique) for a cumulative period ranging from 24 to 240 hours (mean 71).

Patients in whom an intracardiac thrombus was identified and those in whom an embolic event occurred were treated with oral anticoagulants (warfarin). Prothrombin activity or the International Normalised Ratio were maintained at 25%–35% and 3·0–3·9 respectively.

Results

Intracardiac thrombosis was detected at the onset of the study in seven patients and during follow up in other seven. In 13 of these patients the intracardiac thrombosis was mural, while in the remaining patient it was pedunculated and mobile inside the left ventricular cavity. The most frequent site was the apex of the left ventricle (11/14 patients) (fig 1); in one patient the thrombus was localised in the left atrial cavity; in one a small thrombus was attached to the inferior portion of the left side of the intraventricular septum; while in another it was at the level of mitral valve apparatus. In four patients the diagnosis of intracardiac thrombosis by the 3·5 MHz probe was not confirmed by the use of the 5 MHz probe, which showed only the presence of muscular trabeculae or endocardial thickening of the apex.

Embolism occurred in 12 patients (8·4%): seven before they entered the study and five during follow up. The occurrence of new embolic events in patients not taking anticoagulants was 1·4 events for every 100 patient-years. Eleven of 12 patients had systemic embolic events (cerebral in eight, peripheral in two, renal in one) while one patient had a systemic (cerebral) and pulmonary embolism. None of the 14 patients with intracardiac thrombosis had embolism either before entry to the study or during follow up. Conversely no intracardiac thrombosis was found in the 12 patients with embolic complications. There were no statistically significant differences (analysis of variance) in the clinical, echocardiographic, and angiographic findings between the patients with embolic events and those without (table).

Paroxysmal atrial fibrillation was not detected by ambulatory electrocardiographic monitoring in any patient. Non-sustained ventricular tachycardias

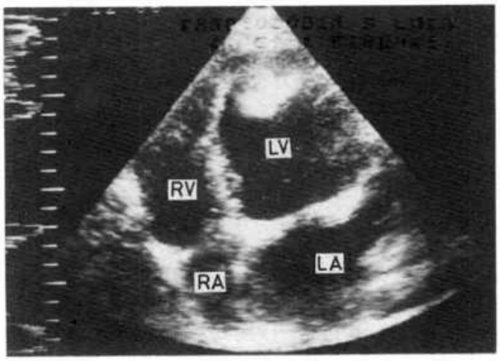

Fig 1 *Cross sectional echocardiogram showing apical four chamber view with an echo-reflecting mass at the apex. LV, left ventricle; LA, left atrium; RV, right ventricle; RA, right atrium.*

Table *Clinical, echocardiographic, and angiographic features in 126 patients with idiopathic dilated cardiomyopathy*

No.	*Sex M/F*	*Age (yr)*	*Status D/A*	*Class NYHA I/II/III/IV*	*ECG SR/AF*	*D%*	*Echo DD (mm)*	*Angio* EF%*
(*a*) 14	13/1	46–67 (56·3)	3/11	0/6/5/3	12/2	6–21 (15·0)	67–87 (76·5)	16–45 (30·0)
(*b*) 12	8/4	36–71 (55·0)	7/5	0/7/5/0	8/4	8–21 (13·2)	62–87 (72·0)	15–34 (24·0)
(*c*) 126	94/32	19–72 (54·0)	33/93	6/67/41/12	111/15	6–25 (15·9)	47–89 (69·5)	7–45 (30·1)

(*a*) Patients with intracavitary thrombosis. (*b*) Patients who had embolic complications. (*c*) Total. D, dead; A, alive; SR, sinus rhythm; AF, atrial fibrillation; D%, fractional shortening of the left ventricle; DD, end diastolic diameter; EF, ejection fraction. *Angiocardiography was performed in 9/14 cases (group a), 4/12 (group b), 62/126 (group c). Mean values are given in parentheses.

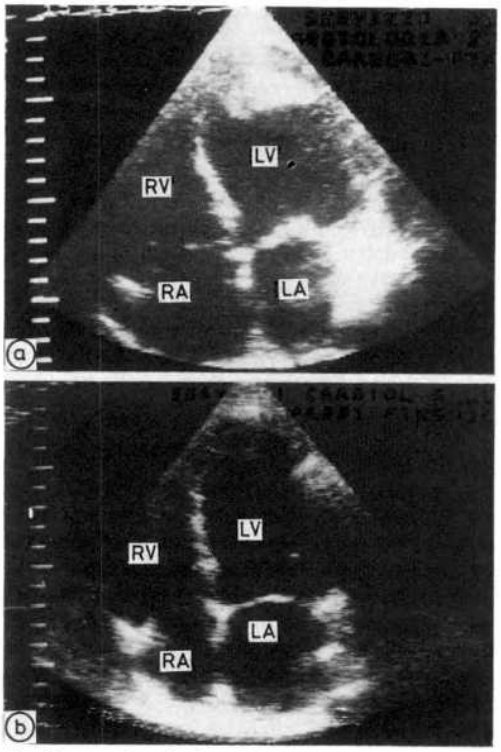

Fig 2 *Cross sectional echocardiogram of apical four chamber views showing (a) a large apical thrombus and (b) no evidence of the thrombus after treatment with oral anticoagulant. LV, left ventricle; LA, left atrium; RV, right ventricle; RA, right atrium.*

occurred in 54% of 11 with embolism and 49% of 101 without.

ANTICOAGULANT TREATMENT

Oral anticoagulants were given to 35 patients—14 with intracardiac thrombosis, 12 with embolism, and nine who were in class IV of the New York Heart Association—either at entry to the study or during it. The cumulative period of treatment was 61 patient-years and the cumulative observation period, from January 1980 to September 1987, was 418 patient-years for the 126 patients with dilated cardiomyopathy. No embolic or haemorrhagic complications were seen during anticoagulant treatment. Intracardiac thrombosis disappeared in two patients one and three months after the start of anticoagulant treatment (fig 2).

Discussion

Systemic embolism is a life-threatening complication in patients with dilated cardiomyopathy and treatment with oral anticoagulants has been recommended[5] particularly during prolonged bed rest, and in patients with heart failure or atrial fibrillation.[6 7] The presence of intracardiac thrombosis, detected by cross sectional echocardiograms, does not seem to be useful in defining a high risk population. Gottdiener *et al* found no statistical difference in the frequency of embolism in a group with intracardiac thrombosis and a group without.[1] Our results confirm their results, although we also found no overlap between the two groups.

We found intracardiac thrombosis in 11·1% of our patients whereas others reported values ranging from 35% to 58% in patients with ischaemic[8] or primary[1] cardiomyopathy examined by cross sectional echocardiography. Our result resembles that found in two necropsy series.[9 10] Exceptionally Tobin *et al* found only one patient with left ventricular thrombus among 90 patients with congestive myocardial disease, half of whom had idiopathic cardiomyopathy.[11] They did not find intracardiac thrombosis on gross inspection in any of the chambers in 27 hearts after death. The cross sectional echocardiographic technique may also influence the results. The 5 MHz transducer that we used in patients in whom an examination with the 3·5 MHz probe suggested an intracardiac thrombus allowed better identification of the left ventricular apex,[12] and excluded false diagnosis of intracardiac thrombosis in four patients. Also the rate of embolic complications was lower in our study (8·4%) than in those reported by Gottdiener *et al* (11%),[1] Fuster *et al* (18%),[13] and Gavazzi *et al* (18%).[14] In Fuster *et al*'s study 3·5 new embolic events occurred every 100 patient-years in patients not treated with anticoagulants,[13] in comparison with 1·4 events for the same period in the present series. The difference in the population studies according to the severity of the disease may be responsible for these results. For instance survival rate was 88% in our study at two years and 56% at five years, while in the Mayo Clinic series it was respectively about 50 and 30%.[13]

Only one of our patients had a protruding left ventricular thrombi; increased motility was reported to promote embolism in patients with ischaemic heart disease.[2,15,16] A mobile thrombus was reported in 27–58% of the patients in these studies. Gottdiener *et al* did not find similar results in patients with idiopathic dilated cardiomyopathy. They reported that the shape of the thrombus (flat or pedunculated) did not influence the occurrence of embolism.[1]

The pathophysiology of thrombus formation and embolisation are notably different in patients with "ischaemic cardiomyopathy"[17] and in those with idiopathic dilated cardiomyopathy.[2] The endocardial abnormalities that stimulate clot formation in acute infarction and chronic aneurysm (for example stasis of blood in the cardiac apex (fig 1)) are different or absent in patients with idiopathic dilated cardiomyopathy.

An intracardiac thrombus disappeared during anticoagulant treatment in two of our patients (fig 2). Treatment with oral anticoagulants, which were also given to five patients during follow up as soon as the embolic event occurred, might have led to the rapid resolution of the intracardiac thrombosis before the echocardiogram was performed,[18] thus further reducing any possible correlation of the two events in this subgroup.

Although atrial fibrillation has been claimed by some to be an important influence on the incidence of embolisation in patients with dilated cardiomyopathy, others did not confirm this view.[17,19,20] In our series embolic complications occurred in 4/15 patients with atrial fibrillation and in 7/11 patients in sinus rhythm. The small number of cases precludes any statistical analysis. Data obtained from the ambulatory electrocardiographic monitoring suggest that non-sustained ventricular tachycardias do not influence the embolic events.

Finally, haemodynamic factors do not seem to correlate with the likelihood of embolism in patients with dilated cardiomyopathy.[1] We found no difference in the echocardiographic left ventricular dimensions or in the ejection fraction among the groups with embolic complications, intracardiac thrombosis, and the whole group (table).

We conclude that anticoagulant treatment may not be needed by every patient with dilated cardiomyopathy but should be given to patients with severe heart failure, previous embolism, and intracavitary thrombosis.

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Diurnal variation of pulmonary artery pressure in chronic heart failure

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SUMMARY Variation in pulmonary artery pressure has important consequences for the interpretation of isolated pressure measurements in patients with chronic heart failure. To investigate the nature of diurnal variation in pulmonary artery pressure in chronic heart failure, eight angina-free men (aged 50–72 years) with treated chronic heart failure caused by ischaemic heart disease underwent continuous ambulatory pulmonary artery pressure recording by a transducer tipped catheter. The mean (1 SD) daytime pulmonary artery pressure was 29·6 (5·0) mm Hg systolic and 13·7 (5·6) mm Hg diastolic. The mean change in pressure from day to night was +5·1 (3·2) mm Hg systolic and +3·8 (1·7) mm Hg diastolic; and the mean change from standing to lying +9·3 (2·3) mm Hg systolic and +6·4 (2·1) mm Hg diastolic. In six of the eight patients there was considerable rise in pulmonary artery pressure at night, but in the two patients with the most severe symptoms there was no nocturnal rise.

In patients with chronic heart failure, nocturnal pulmonary artery pressure is not determined by postural change alone. But interpretation of isolated pulmonary artery pressure measurements must take the posture of the patient into account.

The measurement of central haemodynamic function on a single occasion in patients with chronic heart failure may be affected by the time of day. Haemodynamic changes that could be interpreted as being advantageous in patients with chronic heart failure have been shown on placebo treatment,[1] and after meals.[2] This issue was highlighted when invasive studies showed an improvement in haemodynamic function over 24 hours without any therapeutic intervention.[3]

One possible explanation for these observations is that there is diurnal variation of central haemodynamic function that is confounding their interpretation. We investigated this hypothesis by measuring changes in pulmonary artery pressure in ambulant patients with chronic heart failure over a 24 hour period.

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Patients and methods

PATIENTS

Eight men (mean age 62; range 50–72) with chronic heart failure caused by ischaemic heart disease underwent continuous ambulatory pulmonary artery pressure measurement. They had been admitted to hospital for treatment of heart failure. All had undergone cardiac catheterisation and angiography on a previous hospital admission.

Their principal complaint was breathlessness on exertion and to a lesser extent tiredness. None of the patients had peripheral oedema, angina, or evidence of myocardial ischaemia on the electrocardiogram during exercise. The table shows details of individual patients. Three patients had previously undergone coronary artery surgery (cases 1, 5, and 7). Patients 1 and 6 were taking captopril 25 mg three times a day, and the other patients were taking a dose of amiloride (5 mg or 10 mg/day). None of the patients was being treated with antiarrhythmic drugs, nitrates, calcium antagonists, non-steroidal anti-inflammatory agents, steroids, or anticoagulants.

Table *Data on patients*

Patient	*Age*	*NYHA class*	*Vo_2 max*	*Rest LVEF*	*Exercise LVEF*	*Pillows at night*	*Frusemide dose (mg)*
1	72	2	12·8	45	42	2	80 × 1
2	64	3	11·2	17	16	2	80 × 2
3	60	3	14·0	25		5	80 × 1
4	60	1	15·3	11	15	2	80 × 1
5	68	2	11·3	31		4	40 × 1
6	50	2	14·6	14	18	3	40 × 1
7	61	3	10·4	14	12	2	80 × 2
8	64	3	11·5	16	16	5	80 × 2

NYHA, New York Heart Association; Vo_2 max, maximum rate of oxygen consumption on exercise (ml/kg/min); LVEF, % radionuclide left ventricular ejection fraction.

All of the patients had a cardiothoracic ratio of >0·5 without evidence of pulmonary oedema on a posterior–anterior chest radiograph. They had a normal forced expiratory volume and a normal vital capacity. The mean (1 SD) radionuclide left ventricular ejection fraction for the group was 21·6 (10·7)% at rest and 21·0 (12·6)% on exercise (data from patients 1 and 7 were not available on exercise). The mean right ventricular ejection fraction was 25·1 (8·3)% at rest and 24·3 (10·8)% on exercise. The mean maximum rate of oxygen consumption on exercise was 12·6 (1·7)% ml/kg/min.

PRESSURE MEASUREMENT AND RECORDING

Pulmonary artery pressure was recorded by a 6F micromanometer-tipped catheter (Gaeltec). The signal was amplified with a portable battery driven amplifier and a frequency modulated signal was recorded on tape. In patients 1, 5, and 6 recordings were made on an Oxford Medilog II miniature cassette recorder that was modified by the insertion of a frequency modulator. In patients 2, 3, 4, 7, and 8 recordings were made on a Hewlett Packard 3964A Instrumentation Recorder to which the patient was attached by a 7 m coaxial cable.

The catheter and amplifier had a linear response to pressure over the range 0 to 225 mm Hg (−150 mV to +500 mV) with a correlation coefficient of 0·9997. The frequency response of the catheter plus amplifier was flat from 0 to 14 Hz (−3 dB). The frequency response of the recording and playback equipment was higher than this. The sensitivity of the catheter was 5 μV/V/mm Hg and the maximum hysteresis error was 0·1% of full scale. The temperature coefficient of sensitivity was −0·06%/°C and of zero was 0·01% of full scale. Zero drift of the catheter, amplifier, and recorders was less than 2% of full scale over 24 hours.

After being sterilised in Cidex (Surgikos), the catheter was washed and soaked in physiological saline. Immediately before we inserted the catheter into a patient, we calibrated the system by sealing the catheter tip in a sterile plastic cylinder that was attached via a sterile tube to a 239P air-operated dead-weight pressure balance (Budenberg Gauge Company). Static pressure calibrations were recorded on tape and read off a voltmeter at 0, 1·5, 2·5, 5·0, 7·5, and 10·0 kPa (1 kPa = 7·5006 mm Hg). This calibration procedure was repeated immediately after the catheter was removed from a patient and the calibration lines were used to confirm the absence of a change in catheter sensitivity and to extrapolate the pulmonary artery pressures from the recordings.

STATISTICAL ANALYSIS

The tape recordings of pulmonary artery pressure were replayed on to an ink jet chart recorder (Siemens-Elema Mingograf 82). The systolic and diastolic pressures were sampled every 12 minutes and plotted on a graph (figs 1 and 2). To take account of respiratory variation, the mean systolic and diastolic pressures were determined manually over a 30 second period.

The 24 hour period was divided into day and night for each individual according to the time at which they recorded retiring to bed in the evening and getting out of bed the following morning. The systolic and diastolic pressures were averaged for these periods and compared by a Student's paired *t* test.

PROTOCOL

The patients gave written informed consent to this procedure, which was approved by the National Heart and Chest Hospitals ethics committee.

For the day preceding catheterisation and during the study the patients kept a diary of their activities. The severity of any symptoms experienced was recorded on a visual analogue scale.

The patients fasted for four hours before catheterisation. No premedication was given. In the catheterisation laboratory a 7F introducer was inserted into a subclavian vein under local anaesthetic and through this the catheter was inserted and located, under *x* ray screening, in either the proximal left or right pulmonary artery. The introducer was then withdrawn

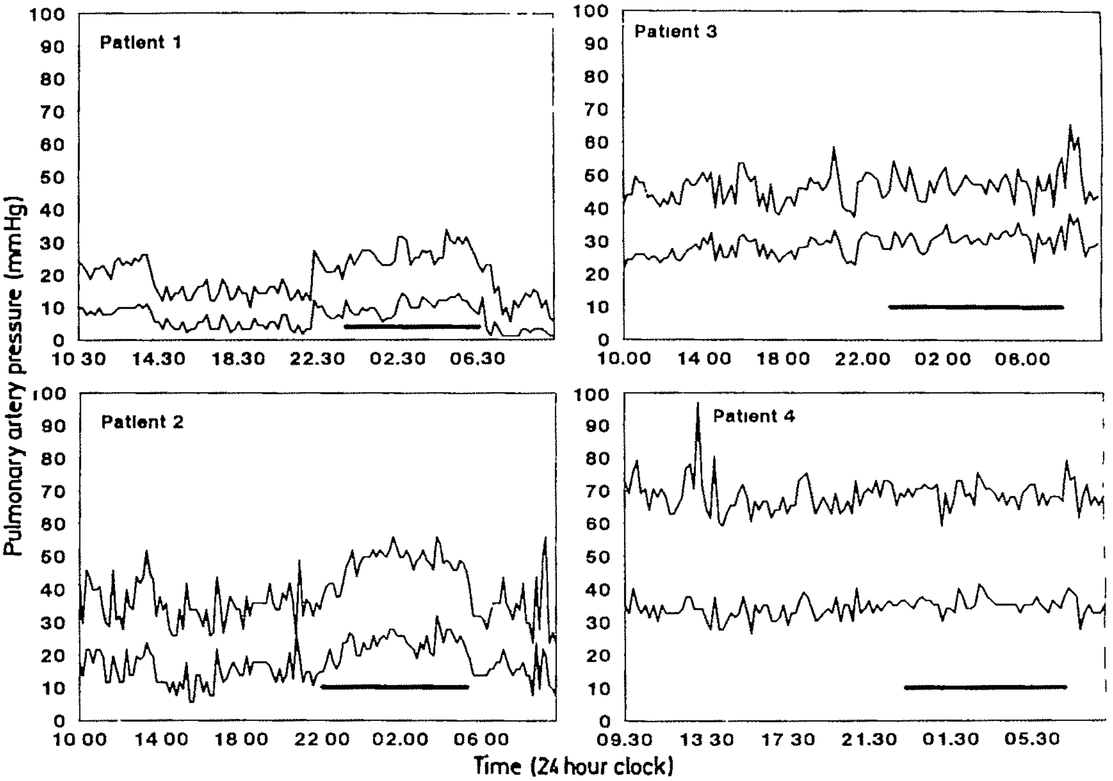

Fig 1 *Twenty four hour recordings of systolic and diastolic pulmonary artery pressure in patients 1 to 4. The time the patient was in bed overnight is indicated by a thick line.*

and the catheter was stitched in place to the skin. Pressure recording was started within 30 minutes of catheter insertion.

On their return to the general ward the patients were fed and those patients catheterised in the morning took their diuretics. The patients on twice daily diuretics received their second dose at 14.00 h. The two patients on captopril took the first dose with their diuretics, the second dose at 14.00 h, and the third dose at 22.00 h. On the second and subsequent days the first dose of drugs was administered at 08.00 h. The patients were encouraged to go about their normal daily activities within the confines of the ward and adjacent staircase. Two organised activities were performed between 14.30 h and 16.00 h during the afternoon of the day of catheterisation. These were a period of recording the postural changes in pressure followed by a walk on the treadmill at a comfortable walking pace for the patient. Pressure was recorded with the patient in different postures for 10 minutes each: lying down on a bed with one pillow, sitting on the edge of the bed, and standing up.

The electrocardiogram was recorded simultaneously with a Oxford Medilog II frequency modulated recorder to screen for arrhythmias and ST segment changes during the period of pressure recording.

Results

All but one of the patients underwent catheterisation in the morning. In patients 1 to 4 the systolic and diastolic pulmonary artery pressures were recorded for 24 hours (fig 1) and in patients 5 to 8 for 48 hours (fig 2).

For the whole group the mean daytime systolic pulmonary artery pressure was 29·6 (5·0) mm Hg and diastolic pressure was 13·7 (5·6) mm Hg. During the night the systolic pressure rose to 36·0 (4·1) mm Hg ($p < 0.005$) and the diastolic to 17·6 (2·9) mm Hg ($p < 0.001$). The mean increase in systolic pressure from day to night was 5·1 (3·2) mm Hg and from standing to lying was 9·3 (2·3) mm Hg ($p < 0.025$). The mean increase in diastolic pressure from day to night was 3·8 (1·7) mm Hg and from standing to lying was 6·4 (2·1) mm Hg ($p < 0.025$).

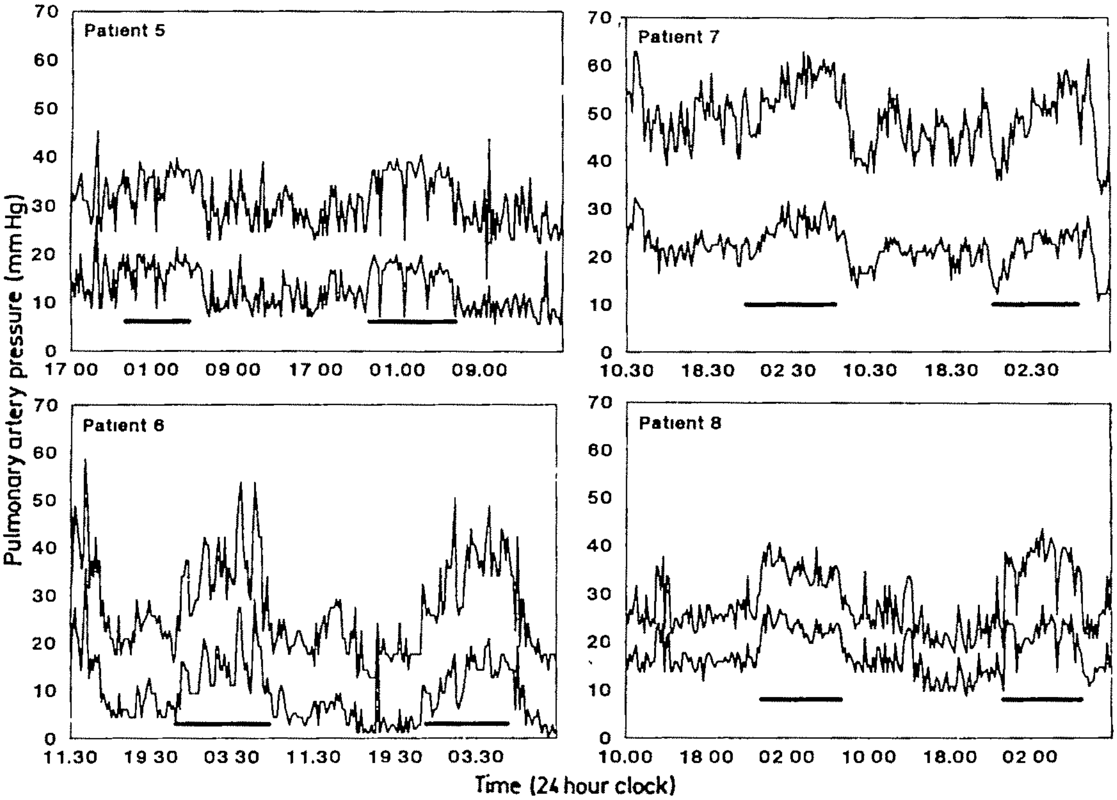

Fig 2 *Forty eight hour recordings of systolic and diastolic pulmonary artery pressure in patients 5 to 8. The time the patient was in bed overnight is indicated by a thick line.*

In six of the eight patients there was considerable diurnal variation in pulmonary artery pressure. In four of these patients recordings were obtained over 48 hours and the diurnal variation in the first 24 hours was similar to that in the second 24 hours. In two of the eight patients (cases 3 and 4) there was no pressure rise during the night. These patients had the worst symptoms, though they had no other features that distinguished them from those whose pulmonary artery pressure showed diurnal variation.

One possible explanation for the nocturnal rise in pressure might be postural change. Comparison of the changes in systolic and diastolic pressure from day to night and lying to standing (figs 3 and 4) shows a change in the same direction with a small but statistically significant difference in the magnitude of the day to night and lying to standing changes. No correlation was found in individuals between postural pressure changes and nocturnal increases in either systolic or diastolic pressure. There was also no correlation between the nocturnal rise in pressure and the number of pillows with which patients slept (table).

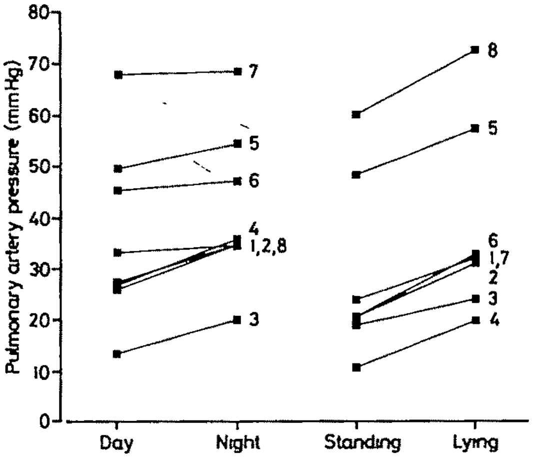

Fig 3 *Comparison of day to night changes in systolic pulmonary artery pressure with changes recorded from standing to lying during the afternoon. Individual patients are numbered.*

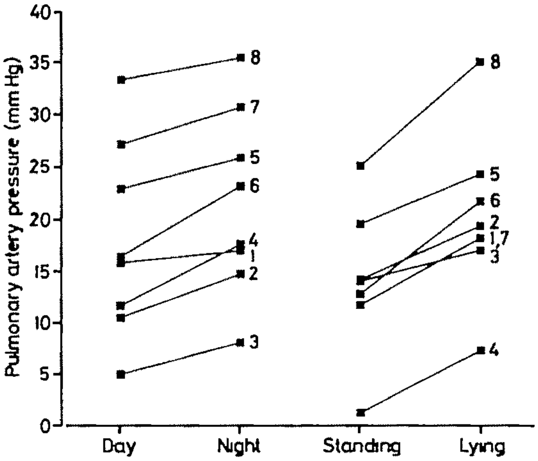

Fig 4 *Comparison of day to night changes in diastolic pulmonary artery pressure with changes recorded from standing to lying during the afternoon. Individual patients are numbered.*

Monitoring of the electrocardiogram showed no ST segment changes and no sustained rhythm disturbance. During the period of recording the patients noted few episodes of breathlessness or tiredness: these were rated as mild. Apart from slight discomfort at the site of catheter insertion, which did not restrict the activity of the patients, there were no complications from the catheterisation procedure.

Discussion

We have shown a considerable variability in pulmonary artery pressure throughout the day: six out of the eight patients showed a substantial rise in pulmonary artery pressure while they were in bed at night. Despite the invasive nature of the investigation, the patients stated they were almost as mobile as they were at home and all reported sleeping well. For the whole group the mean pulmonary artery systolic and diastolic pressures at rest were within normal limits during the day but became abnormal at night. In the 48 h recordings the same pattern of pressure rise was reproduced each night. Pulmonary artery pressure may be affected by left ventricular function,[4,5] exercise, effects of diuretics,[6] meals,[2,7] respiratory pattern,[8-10] autonomic effects such as fear,[11-13] and temperature.[14] It seems that the previous inconsistences in the assessment of pulmonary artery pressure could be explained by these effects together with diurnal and postural changes.[15-17] The effect of drugs on the behaviour of the pulmonary artery pressure in our patients cannot be quantified, but it is likely that they are partially responsible for the variability that we saw.

The use of micromanometer tipped catheters for extended pressure measurement overcomes many of the problems inherent in fluid-filled systems such as errors in transducer balancing, calibration and levelling to the zero reference point, as well as artefacts such as catheter whip, catheter impact, and end pressure.[18] Micromanometer catheters have their own shortcomings, in particular, zero drift, temperature sensitivity, and fragility. The studies in our eight patients did not seem to be hampered by these problems.

There is only limited information about normal diurnal variation of pulmonary artery pressure. In ten normal individuals who underwent polygraphic monitoring pulmonary artery pressure rose significantly, from an average of 18/8 mm Hg while awake to 23/12 mm Hg during sleep.[19] Diurnal variation of pulmonary artery diastolic pressure in patients with chest pain showed a significant rise in pressure between midnight and 06.00 h.[20]

The changes that we saw in pulmonary artery pressure in patients in bed at night are largely consistent with a change in posture. The discrepancy between standing to lying and day to night pressure changes may be explained either because the patients were propped up on more pillows at night than they were when they lay down during the day or because postural pressure changes themselves varied according to the time of day itself and to the timing of drug administration.

Two further observations, however, suggest that the nocturnal pressure rise cannot be explained entirely by posture. First, the rise in pressure at night was not always sudden and it varied considerably. In four of the patients (cases 1, 2, 6, and 7) the nocturnal rise in pressure was of gradual onset and tended to increase during the night. This is in contrast with the postural pressure changes during the day which took less than 15 seconds to equilibrate at their new value and then remained steady. Second, two patients had no nocturnal rise in pressure. Their posture at night did not differ from that of the other patients and they had similar postural pressure changes during the day compared with the rest of the group.

Sleep itself is probably not responsible for the pressure changes because hypnosis had no effect on cardiac output or pulmonary vascular pressures.[21] In studies of neural control of pulmonary artery pressure in patients with heart failure treated with ganglionic and sympathetic blocking agents a fall in pulmonary artery pressure was recorded during sleep.[22] This finding may have reflected the use or consumption of the drugs.

In patients with treated chronic heart failure, there is often diurnal variation of pulmonary artery pressure, the notable feature of which is a pronounced pressure rise at night. Superimposed upon this are other sources of temporary variation such as posture, alterations of which may cause large pressure changes. Although lying down may have been the principal cause of the nocturnal rise in pulmonary artery pressure seen in six of our eight patients, the pattern of a gradual rise in pressure in some of these patients and the lack of nocturnal rise in pressure in a further two patients suggest that other unexplained factors may influence the pulmonary artery pressure at night, and that different mechanisms may predominate in different individuals. Patients with chronic heart failure and a nocturnal increase in pulmonary artery pressure may be at increased risk of developing paroxysmal nocturnal dyspnoea.

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Influence of naloxone on the effects of high frequency transcutaneous electrical nerve stimulation in angina pectoris induced by atrial pacing

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SUMMARY The influence of naloxone on the effects of high frequency transcutaneous electrical nerve stimulation in angina pectoris induced by atrial pacing was studied in 11 patients with severe coronary artery disease. The patients were catheterised and treated with transcutaneous electrical nerve stimulation on two occasions, double blind and in random order, with a single intravenous dose of saline or with a single intravenous dose of 50 mg naloxone. Treatment with transcutaneous electrical nerve stimulation increased tolerance to pacing and significantly improved lactate metabolism with placebo and with naloxone. The positive effects of transcutaneous electrical nerve stimulation were thus reproducible and not reversed by single intravenous doses of naloxone.

The results indicate that the effects of transcutaneous electrical nerve stimulation on the heart are not mediated by β endorphin but they do not exclude activation of more short-acting opioids such as δ or κ receptor agonists (met-enkephalin or dynorphin or both) because naloxone has a low affinity for these receptors. Non-opioid mechanisms may also be important.

High frequency transcutaneous electrical nerve stimulation was reported to be beneficial in patients with angina.[1 2] In one study, transcutaneous electrical nerve stimulation increased work capacity during a bicycle ergometer test, decreased ST segment depression at a comparable workload, and reduced the recovery time.[1] In an invasive study, transcutaneous electrical nerve stimulation increased tolerance to pacing, improved lactate metabolism, and reduced ST segment depression.[2] A decrease in left ventricular afterload caused by a drop in systolic blood pressure was thought to be one explanation for the effects.

Several studies have indicated that the effect of transcutaneous electrical nerve stimulation treatment may be due to activation of endogeneous opioid peptides.[3 4] If this is true, naloxone, a pure opiate antagonist with no agonistic properties, might abolish the effects induced by transcutaneous electrical nerve stimulation.

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Patients and methods

PATIENTS

Eleven patients (two women and nine men aged 50–71 years (mean 61 years)) were chosen from among those visiting the outpatient clinic at the medical department, Östra Hospital. All patients had severe angina (functional class III–IV New York Heart Association) despite their taking optimal antianginal medication. No patients had obstructive or restrictive pulmonary disease, intermittent claudication, valvar heart disease, or untreated hypertension. Eight patients had had a myocardial infarction more than six months before the study. All patients had chest pain and ST segment depression (0·1–0·7 mV) during a maximal symptom limited bicycle ergometer test. On scintigraphic examination, ischaemia of the anterior wall of the myocardium was seen in 10 patients when thallium was injected during exercise testing. All patients had been considered for bypass operation: four patients had been operated on but still had disabling angina pectoris, and one was waiting for operation. Four of these patients had three vessel disease, one had two vessel disease, and one had single vessel disease.

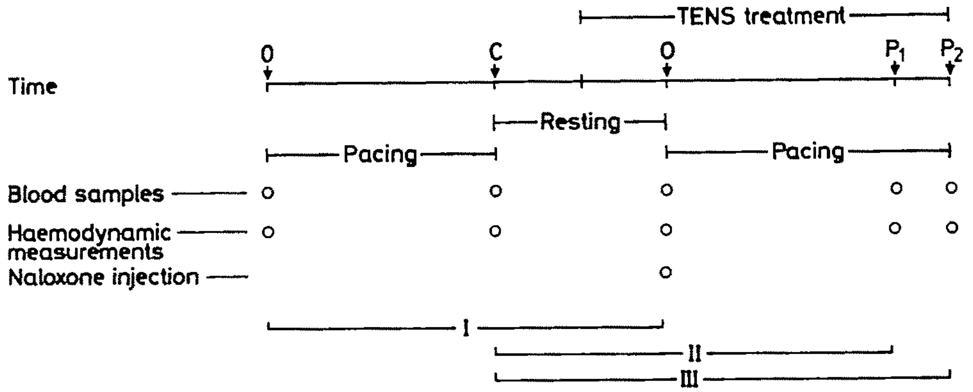

Figure *Schedule, procedures, and statistical comparisons. Roman numerals I to III refer to tests of paired data (see statistical analysis). O, start of pacing; C, maximum pacing without transcutaneous electrical nerve stimulation (TENS) (control); P_1, pacing to identical heart rate as C; P_2, maximum pacing with transcutaneous electrical nerve stimulation.*

Six patients were considered unsuitable for bypass operation. No patient had signs of pulmonary congestion on radiological examination of the heart.

No antianginal medication was given 12 hours before the pacing procedures and no transcutaneous electrical nerve stimulation treatment 48 hours before the trials. The patients were studied in the morning in a non-sedated, fasting state.

The study was approved by the ethics committee of the University of Gothenburg. Oral and written information about the study was given to every patient.

CATHETERISATION

A thermodilution pacing catheter (Wilton-Webster Laboratory) was placed in or near the great cardiac vein within the coronary sinus. If blood could not be sampled from this site, the catheter was pulled back until the backflow was adequate. The position of the catheter was confirmed by injection of radio-opaque dye and was adjusted during flow measurement until a satisfactory stable baseline flow curve was obtained. To exclude reflux from the right atrium a bolus dose of saline was injected into the right atrium while temperature was measured in the coronary sinus.

A catheter was placed percutaneously in a peripheral artery.

MEASUREMENTS

Coronary sinus blood flow was measured by the continuous infusion thermodilution method[5] and isotonic saline solution was therefore infused into the coronary sinus at a rate of 40 ml/minute. Pressures were measured by means of Statham P23 DA transducers and stored on tape for subsequent automatic data processing. Cardiac output was measured by the thermodilution technique (Cardiac Output Computer, WT1). Blood oxygen saturation was measured by an OSM 2 Hemoxymeter (Radiometer, Copenhagen). Lactic acid concentration was assayed enzymatically (Lactate Analyzer 640, Roche Bio-Electronics). Plasma concentrations of adrenaline and noradrenaline were assayed radioenzymatically by the method of Peuler and Johnson, slightly modified by Eriksson.[6]

TRANSCUTANEOUS ELECTRICAL NERVE STIMULATOR AND STIMULATION TECHNIQUE

A commercially available transcutaneous nerve stimulator (Neurostal) was used. The stimulator delivers constant current in 0·2 ms pulses and the frequency was set to 70 Hz. Standard electrodes (3M; Tenz Care 6225, 15 × 50 mm) were used. Electrode paste was applied to the contact surface to reduce the skin-electrode impedance. The electrodes were placed 10 to 30 cm apart on the chest of the patient at the site of the most intensive pain. The intensity of the stimulation was adjusted to a level immediately below that producing pain (35 to 50 mA).

PROCEDURE

The patients were studied twice (double blind and in random order): once after a single intravenous dose of 120 ml saline and once after a single intravenous dose of 50 mg naloxone dissolved in 120 ml physiological saline (figure). The interval between the investigations was two to seven days.

Blood samples were drawn from a peripheral artery and the coronary sinus at rest during steady state. Blood pressure and coronary sinus blood flow were measured simultaneously. Coronary sinus pacing was then started at a rate of 80 beats/minute. One patient was started at 90 beats/minute and two patients at 100 beats/minute because of a high resting heart rate. The pacing rate was increased by 10 beats/minute every minute, continuing until the patient could not tolerate a further increase in pain. New measurements and blood samples were taken. Pacing was then stopped. After 25 minutes rest without pacing, transcutaneous electrical nerve stimulation treatment was started. Fifteen minutes later, new baseline measurements and blood samples were taken. After another five minutes the same pacing routine was repeated and repeat measurements were made at the same pacing rate as that at which angina had been produced during the previous control recording. Exactly five minutes before the repeat measurements a single dose of 50 mg naloxone or the equivalent amount of saline as placebo was given by infusion, double blind in random order. The pacing was not interrupted during infusion of naloxone or physiological saline. The pacing rate was then increased until the patient considered the chest pain to be as intense as it was during control registration before treatment with transcutaneous electrical nerve stimulation. New pressure recordings and blood samples were then taken (figure). If the patient did not experience chest pain, pacing was stopped at 170 beats/minute.

CALCULATIONS

Coronary vascular resistance (mm Hg/ml/min) was estimated as mean arterial blood pressure divided by coronary sinus blood flow. The myocardial oxygen consumption (ml/min) was calculated as the myocardial arteriovenous oxygen difference multiplied by coronary blood flow. The myocardial lactate extraction ratio (%) was expressed as 100 × (arterial lactate concentration − coronary sinus lactate concentration) divided by the arterial lactate concentration.

The myocardial arteriovenous difference for adrenaline reflects its extraction from the coronary circulation, because only the brain and the adrenal medulla can synthesise and release adrenaline.[7] Thus adrenaline (A) uptake (nmol/min) equals the arteriovenous difference in adrenaline × coronary sinus blood flow. In addition to being extracted from the coronary circulation, noradrenaline is also released from sympathetic nerve endings and the myocardial arteriovenous difference in noradrenaline is thus the result of a combined uptake and release of the catecholamine and will be referred to as "noradrenaline overflow" (nmol/min), which equals the arteriovenous difference × coronary sinus blood flow. Adrenaline and noradrenaline share the same uptake mechanisms and the extraction ratio seems to be similar as well,[7] so noradrenaline uptake (nmol/min) can be estimated as: percentage adrenaline uptake × coronary sinus blood flow × noradrenaline arterial concentration. Net myocardial noradrenaline release can be calculated by assuming that the inflow of noradrenaline (coronary sinus blood flow × arterial noradrenaline concentration) + release − uptake = efflux of noradrenaline (coronary sinus blood flow × coronary sinus concentration)—that is noradrenaline release (nmol/min) equals coronary sinus blood flow × (coronary sinus − arterial noradrenaline concentration) + noradrenaline uptake.

Time to angina (seconds) was calculated as the time from the start of atrial pacing until pain and recovery time (seconds) as the time after the pacing was stopped until pain disappeared.

STATISTICAL METHODS

We used the difference between the corresponding values at rest and during pacing to compare saline and naloxone and control and transcutaneous electrical nerve stimulation. Fisher's test for pair comparisons was applied to the differences.[8] All tests were two tailed. Whether or not the differences should be used depends on the correlation coefficient between the baseline value and the current value. If the coefficient exceeds 0·50, it is better to use the difference. Excess of this limit was justified in this study. The results were analysed as follows (figure)—(*a*) resting values were compared with transcutaneous electrical nerve stimulation and without, (*b*) maximal control pacing rates were compared with those at identical heart rates during transcutaneous electrical nerve stimulation, and (*c*) the maximal control values were compared with maximal values during transcutaneous electrical nerve stimulation. Because a large number of tests were performed the risk of finding statistical significance by chance was great. A traditional analysis of variance would have restricted the number of falsely significant results per type of variable to one; such a parametric analysis gives inaccurate p values. Because the number of types of variables was also large, it was more appropriate to test the hypothesis with accurate p values for each variable and use the pattern of statistically significant results to examine the possibility of falsely significant results.

Results

HAEMODYNAMIC AND MYOCARDIAL METABOLIC EFFECTS OF TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION AND PLACEBO (TABLE 1)

Transcutaneous electrical nerve stimulation induced no major changes at rest.

During transcutaneous electrical nerve stimulation at comparable heart rates the mean (1 SD) able 1 *Effects of transcutaneous electrical nerve stimulation (TENS) and placebo at rest and during pacing (mean (SD))*

ariable	*Control rest*	*TENS rest*	*Control pacing to angina*	*TENS pacing$_1$*	*TENS pacing$_2$*
eart rate (beats/min)	74 (14)	77 (19)	134 (18)	134 (18)	146 (22)**
ystolic blood pressure (mm Hg)	154 (30)	160 (20)	155 (24)	159 (20)	155 (25)
iastolic blood pressure (mm Hg)	70 (10)	75 (13)	89 (14)	90 (12)	91 (13)
ean blood pressure (mm Hg)	103 (20)	104 (16)	110 (18)	114 (18)	111 (19)
ate-pressure product (beats mm Hg/min)	11605 (3666)	12537 (4758)	20720 (5419)	21357 (5218)	23085 (5188)
oronary sinus blood flow (ml/min)	104 (43)	118 (46)	194 (49)	208 (76)	255 (135)
Myocardial oxygen consumption (ml O_2/min)	14·6 (7·1)	17·5 (7·9)	26·0 (7·3)	27·5 (8·4)	34·0 (14·8)
Myocardial lactate extraction ratio (%)	13 (12)	15 (7)	−20 (33)	−8 (21)*	−28 (40)
rterial concentrations of adrenaline (nmol/l)	0·44 (0·27)	0·30 (0·10)	0·48 (0·19)	0·41 (0·14)	0·47 (0·18)
rterial concentrations of noradrenaline (nmol/l)	2·0 (0·9)	2·2 (0·6)	2·6 (1·1)	2·7 (0·9)	3·3 (1·3)
alculated net myocardial noradrenaline release (nmol/min)	151 (114)	198 (100)	241 (120)	230 (83)	469 (598)
ime to angina (s)			239 (83)		425 (196)**
ecovery time (s)			164 (230)		49 (63)*

ENS pacing$_1$, same pacing rate as control pacing to angina; TENS pacing$_2$, pacing to angina during TENS; *$p < 0·05$ compared with control pacing to gina value; **$p < 0·01$ compared with control pacing to angina value.

lactate production fell (−20 (3) *v* −8 (21)%; $p < 0·05$). All patients experienced chest pain in both pacing periods, but the tolerance to pacing increased after transcutaneous electrical nerve stimulation (134 (18) *v* 146 (22) beats/min; $p < 0·01$), time to angina increased (239 (83) s *v* 425 (196) s; $p < 0·01$), and the recovery time decreased (164 (230) *v* 49 (63) s; $p < 0·05$). There were no other differences in systemic and coronary haemodynamic function or metabolic effects during pacing to the same heart rate or to maximal heart rate during transcutaneous electrical nerve stimulation compared with control.

For adrenaline and noradrenaline no significant changes occurred during transcutaneous electrical

Table 2 *Effects of transcutaneous electrical nerve stimulation (TENS) and naloxone at rest and during pacing (mean (SD))*

ariable	*Control rest*	*TENS rest*	*Control pacing to angina*	*TENS pacing$_1$*	*TENS pacing$_2$*
Heart rate (beats/min)	74 (13)	75 (15)	135 (14)	135 (14)	148 (20)**
ystolic blood pressure (mm Hg)	162 (30)	164 (29)	155 (28)	152 (21)	140 (8)
astolic blood pressure (mm Hg)	75 (13)	78 (11)	95 (15)	91 (1)	91 (5)
Mean blood pressure (mm Hg)	108 (19)	109 (18)	119 (20)	113 (16)	115 (7)
Rate-pressure product (beats mm Hg/min)	12172 (4035)	12533 (4157)	21234 (5751)	20696 (4540)	21528 (2362)
Coronary sinus blood flow (ml/min)	116 (58)	115 (49)	207 (86)	187 (74)	197 (65)
Myocardial oxygen consumption (ml O_2/min)	16·3 (9·3)	16·1 (6·6)	27·6 (10·2)	25·7 (9·5)	28·0 (8·7)
Myocardial lactate extraction ratio (%)	13 (8)	16 (10)	−28 (35)	−19 (37)**	−31 (31)
Arterial concentrations of adrenaline (nmol/l)	0·40 (0·20)	0·36 (0·13)	0·48 (0·24)	0·53 (0·26)	0·57 (0·12)
Arterial concentrations of noradrenaline (nmol/l)	2·0 (0·7)	2·5 (0·8)	3·0 (1·0)	3·0 (1·1)	3·2 (1·8)
Calculated net myocardial noradrenaline release (nmol/min)	263 (171)	167 (151)	377 (326)	328 (271)	492 (333)
Time to angina (s)			243 (106)		379 (251)
Recovery time (s)			103 (108)		52 (73)**

TENS pacing$_1$, same pacing rate as control pacing to angina; TENS pacing$_2$, pacing to angina during TENS; **$p < 0·01$ compared with control pacing o angina value.

nerve stimulation at rest, during pacing to the same heart rate, or at maximal pacing (table 1).

HAEMODYNAMIC AND MYOCARDIAL METABOLIC EFFECTS OF TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION AND NALOXONE (TABLE 2)

Transcutaneous electrical nerve stimulation induced no changes at rest. During transcutaneous electrical nerve stimulation at a comparable heart rate the mean lactate production decreased (−28) (35) *v* −19 (37)%; $p < 0.01$). All patients experienced chest pain in both pacing procedures, but tolerance to pacing increased after transcutaneous electrical nerve stimulation (135 (14) *v* 148 (20) beats/minute; $p < 0.05$) and the recovery time decreased (103 (108) *v* 52 (73) s; $p < 0.01$). During pacing to maximal heart rate transcutaneous electrical nerve stimulation did not induce any effects.

Transcutaneous electrical nerve stimulation did not result in any significant changes in concentrations of adrenaline and noradrenaline at rest, during pacing to the same heart rate, or during maximal pacing (table 2).

A COMPARISON OF DIFFERENCES BETWEEN TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION PLUS PLACEBO AND TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION PLUS NALOXONE

There were no significant differences, either at rest or during pacing, in any of the variables, including catecholamines when transcutaneous electrical nerve stimulation plus placebo was compared with transcutaneous electrical nerve stimulation plus naloxone.

Discussion

The results of this study indicate that the positive effects of high frequency transcutaneous electrical nerve stimulation in angina induced by pacing—that is increased tolerance to pacing, improved lactate metabolism, and less anginal pain—are reproducible. None of these effects was reversed by naloxone.

Atrial pacing is considered to be a sufficiently reproducible method if the heart rate is quickly increased to the anginal value and a recovery period of at least 20 minutes is allowed between control and treatment sessions.[9 10] The recovery period in the present study was 40 minutes. Transcutaneous electrical nerve stimulation was always given as the second part of the test because transcutaneous electrical nerve stimulation has long term effects that could interfere with control pacing.[2]

Time to angina increased significantly during transcutaneous electrical nerve stimulation and placebo treatment compared with control values. During transcutaneous electrical nerve stimulation and naloxone there was no significant increase of time to angina compared with control. However, when the differences between time to angina during transcutaneous electrical nerve stimulation plus placebo and control were compared with the difference between transcutaneous electrical nerve stimulation plus naloxone and control there was no significant difference. But the presence of a significant difference between transcutaneous electrical nerve stimulation and no stimulation for placebo treatment and the absence of such a difference for naloxone treatment or the converse must not be interpreted as a statistically significant difference between placebo and naloxone.

Opioids have been suggested as mediators of numerous physiological and pathophysiological processes and opiate receptors have been identified in many peripheral organs, including the adrenal medulla, sympathetic ganglia, and the heart.[11 12] The effects of transcutaneous electrical nerve stimulation have been suggested to be at least partly mediated by endogenous opioids.[13] Different frequencies of stimulation are assumed to activate different opioid systems. For example, in one investigation Woolf *et al* found that high frequency transcutaneous electrical nerve stimulation had an opioid-dependent antinociceptive effect in rats that was abolished by naloxone (1 mg/kg).[14] However, other studies showed that low frequency electrostimulation releases β endorphins, which can be blocked by naloxone, while high frequency stimulation, which was used in this study, may release met-enkephalin, which was not blocked by conventional doses of naloxone.[15 16] This may explain why naloxone did not block the effects of transcutaneous electrical nerve stimulation in this study, in which high frequency transcutaneous electrical nerve stimulation was used.

The single intravenous dose of naloxone needed to block the effects of exogenously administered opioids is 0·4–0·8 mg. Cohen *et al* showed that systolic blood pressure and respiratory responses increased with the dose of naloxone in normal adults (0·3 mg/kg–4 mg/kg).[17] They concluded that the lower doses of naloxone previously used in human studies were not sufficient to block completely endogenous opioid systems. Thus despite the high dose of naloxone used in this study (0·7 mg/kg given as a single dose of 50 mg), it might still have been insufficient to block every type of opioid receptor. Naloxone is known to have high affinity for μ receptors.[18] However, the drug only attenuated the response to a δ agonist and was ineffective against the κ agonist, ketazocine.[19] Dynorphin is a potent and selective ligand for κ receptors.[20] In a previous study an increase of dynorphin was found in two patients studied during transcutaneous electrical nerve stimulation at the corresponding pacing rate.[21] Thus if the effects of transcutaneous electrical nerve stimulation are mediated by met-enkephalin or dynorphin, the doses of naloxone used in this study might have been insufficient to block the δ and κ receptors. β Endorphin has high affinity for μ receptors.[22] It therefore seems less likely that the antianginal effects of high frequency transcutaneous electrical nerve stimulation in pacing induced angina are mediated by β endorphin in view of the apparent lack of effect of naloxone in this study. However, it is possible that a more specific δ or κ antagonist blocked the effects of transcutaneous electrical nerve stimulation in the present study.

Evidence suggests that transcutaneous electrical nerve stimulation may influence autonomic systems mainly by suppressing sympathetic overactivity.[23] Evidence from several studies suggests that opioid peptides may act upon cardiovascular receptors.[19] Enkephalin, dynorphin, and the δ and κ opioid receptors have all been shown in guinea pig hearts.[24] It has been suggested that opioid peptides may affect the local modulation of sympathetic cardiac neurotransmission. In general, the opioid systems seem to become active only during pathophysiological conditions such as stress, pain, and hypoxia and they seem to have an inhibitory or modulating influence.[4 25] They are co-stored with catecholamines in sympathetic ganglia and the adrenal medulla and are believed to modify their release and inhibit sympathetic activity.[26] Transcutaneous electrical nerve stimulation was recently found to increase pacing tolerance, improve lactate metabolism, and reduce ST segment depression.[27] These effects were thought to be caused by a decrease in left ventricular afterload, as reflected by a fall in systolic blood pressure secondary to reduced sympathetic activity; this mechanism accords with the fall in arterial concentrations of adrenaline and noradrenaline during transcutaneous electrical nerve stimulation in those who responded to transcutaneous electrical nerve stimulation. However, in this study, there were no changes in arterial catecholamine concentrations or systemic blood pressure during transcutaneous electrical nerve stimulation. Patient population, timing of blood sampling, and the method of analysing catecholamines were exactly the same in the two studies. There were no other methodological problems that could explain the different results obtained.

It is also possible that non-opioid mechanisms are important in mediating the effects of transcutaneous electrical nerve stimulation. For example parachlorophenylalanine, an inhibitor of serotonin synthesis, reduced the analgesic effect of high frequency electroacupuncture in mice whereas naloxone did not.[28] Conversely, naloxone completely reversed the effects of low frequency stimulation but parachlorophenylalanine did not have any effect. There are serotoninergic neurones from the medulla to the spinal dorsal horns. This descending pathway activates inhibitory enkephalinergic interneurones which in turn block the pain signal at the segmental level.[29] High frequency electrostimulation, which is strictly segmental, might activate this inhibitory serotoninergic pathway.

The positive effects of high frequency transcutaneous electrical nerve stimulation in angina induced by pacing—increased tolerance to pacing, improved lactate metabolism, and less angina—were reproducible and not reversed by single intravenous doses of 50 mg naloxone. The effects of transcutaneous electrical nerve stimulation therefore seem not to be mediated by β endorphin, but the treatment might activate more short-acting δ or κ agonists such as met-enkephalin or dynorphin because naloxone has low affinity with these receptors. It is also possible that non-opioid mechanisms are important.

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Colour flow imaging in the diagnosis of multiple ventricular septal defects

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SUMMARY Thirty one patients with multiple ventricular septal defects were studied by cross sectional echocardiography, conventional pulsed and continuous wave Doppler, colour flow imaging, and left ventriculography to determine the relative diagnostic benefits and pitfalls of each technique. The patients studied had a wide range of congenital heart defects with 19 patients having isolated multiple ventricular septal defects, three with associated tetralogy of Fallot, five with double outlet right ventricle, three with complete transposition and ventricular septal defect, and one with a complete atrioventricular septal defect. In 23 patients the defects were inspected at operation. Cross sectional imaging with integrated pulsed and continuous wave Doppler correctly identified multiple defects in only 12 (39%) patients. In contrast, colour flow imaging was accurate in 24 (77%) patients and left ventriculography in 20 (65%) patients. When patients were subdivided on the basis of relative peak systolic ventricular pressures into restrictive defects (18 patients) and non-restrictive defects (13 patients) the diagnostic value of colour flow imaging was different for each group. Colour flow mapping correctly identified multiple ventricular septal defects in 16/18 (89%) patients with restrictive defects but only 8/13 (62%) with non-restrictive defects. The comparative diagnostic accuracy of left ventriculography was 15/18 (83%) in the restrictive group and 5/13 (38%) in the non-restrictive group.

Colour flow imaging was the single investigative technique with the greatest diagnostic accuracy in the diagnosis of multiple ventricular septal defects. It failed to be consistently accurate in defined subgroups with non-restrictive defects as did left ventriculography. The greatest overall diagnostic accuracy in this series was obtained when both colour flow imaging and ventriculography techniques were used in combination in a complementary fashion.

Multiple ventricular septal defects are not uncommon in congenital heart disease. The reported frequency in patients with multiple ventricular septal defects as an isolated lesion ranges from 4% to 18%.[1-3] Multiple ventricular septal defects are more common in patients with double outlet right ventricle,[4] complete atrioventricular septal defects,[5 6] tetralogy of Fallot,[5] and complete transposition with ventricular septal defect.[5]

It is important to make a precise preoperative diagnosis of multiple ventricular septal defects because they are associated with a higher surgical mortality[2 3] and a higher rate of palliative pulmonary artery banding rather than primary repair; failure to make an accurate preoperative diagnosis leads to a high reoperation rate.[7] Traditionally the diagnosis of multiple ventricular septal defects has relied on left ventriculography.[8] Despite recent improvements in this technique such as the introduction of biplane equipment for axially angled projections and the decreased toxicity of contrast agents (allowing multiple injections), the diagnostic accuracy of left ventriculography at best only approaches 86%.[5]

Ultrasound studies have shown that cross sectional echocardiography can visualise most moderate to large defects especially when they are sited in the perimembranous and the smooth muscular inlet septa.[9] However, small defects both single and mul-

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tiple within the trabecular and muscular outlet septa have proved difficult to visualise by cross sectional imaging alone.[9] The addition of pulsed Doppler to ultrasound systems has improved the diagnosis of small defects by identifying the diagnostic disturbances of transseptal and right ventricular flow associated with these defects.[10] Although it has been suggested that multiple defects can be detected by a right ventricular and septal scanning technique with pulsed Doppler,[10] others have shown that such an integrated technique of cross sectional imaging and pulsed Doppler scanning can be inaccurate in the diagnosis of multiple ventricular septal defects.[11] Both pulsed and continuous wave Doppler techniques are inadequate where non-restrictive ventricular septal defects are present. These result in low transseptal flow velocities and a laminary flow across the defect,[10] in contrast with the high velocity turbulent flow associated with restrictive defects.

Colour flow imaging was a useful technique for the diagnosis of single restrictive ventricular septal defects because it allowed visualisation of their characteristically turbulent transseptal and right ventricular flow patterns.[12] Previous work using colour flow imaging in the diagnosis of multiple ventricular septal defects (mainly confined to restrictive defects) suggested both a high sensitivity and specificity for their detection.[11] However, no direct comparison between the predictive value of colour flow imaging and left ventriculography could be made in the reported series, because only patients with multiple ventricular septal defects previously identified by left ventriculography were studied. Also no comparison was made between the diagnostic role of colour flow imaging in groups with restrictive and non-restrictive defects.

The aims of the present study were to evaluate the usefulness of colour flow imaging in the diagnosis of all types of multiple ventricular septal defects, to compare this prospectively with the diagnostic accuracy of left ventriculography, and to define any inherent limitations in the technique.

Patients and methods

STUDY PATIENTS AND TYPE OF VENTRICULAR SEPTAL DEFECT

Between June 1986 and October 1987, 31 infants and children (aged 2 days to 11 years, mean 2·11 years) with multiple ventricular septal defects diagnosed at the Wessex Paediatric Cardiac Unit were investigated by angiography, cross sectional echocardiography, and colour flow imaging. Nineteen patients had isolated multiple ventricular septal defects, 11 of whom had a combination of perimembranous and muscular defects, six had multiple discrete muscular defects, and two had "Swiss cheese" defects. Of the 12 with ventricular septal defects occurring as part of a complex congenital lesion included in the series, three patients with tetralogy of Fallot and three patients with double outlet right ventricle had a combination of a perimembranous outlet plus muscular ventricular septal defects. Two further patients with double outlet right ventricle had non-committed multiple muscular defects. Three patients with complete transposition and multiple ventricular septal defects had a combination of a single perimembranous plus a muscular defect and the patient with a complete atrioventricular septal defect had an associated muscular defect (table 1).

Patients were entered into the study only if an unequivocal diagnosis of multiple ventricular septal defects was first made by: (*a*) an unequivocally diagnostic left ventriculogram (16 patients), (*b*) cross sectional imaging plus positive colour flow imaging (10 patients), and (*c*) surgical inspection (five patients had multiple ventricular septal defects identified for the first time at operation). All patients then underwent any of the other preoperative investigations not already undertaken, so that every patient in the study had available for review cross sectional echocardiography with conventional Doppler studies, colour flow imaging studies, and left ventriculography. The five patients whose diagnosis of multiple ventricular septal defects was first made at operation all had preoperative left ventriculograms, cross sectional imaging, and conventional Doppler and colour flow studies, which were then reviewed. To date a total of 23 patients have had surgical closure of their ven-

Table 1 *Morphological diagnosis versus type of ventricular septal defect*

Morphological diagnosis	*Restrictive*		*Non-restrictive*		
	Defect type	*No*	*Defect type*	*No*	*Total*
Isolated VSDs	PMO + musc	11			
(no other lesion)	Mult musc	5	Mult musc	1	19
			"Swiss cheese"	2	
Tetralogy of Fallot		0	PMO + musc	3	3
DORV		0	PMO + musc	3	
			Mult musc	2	5
TGA/VSD	PMO + musc	1	PMO + musc	1	
	PMI + musc	1			3
CAVSD		0	PMI + musc	1	1
Total		18		13	31

VSD, ventricular septal defect; PMO + musc, perimembranous outlet plus muscular defects; Mult musc, multiple muscular defects, PMI + musc, perimembranous inlet plus muscular defects; DORV, double outlet right ventricle; TGA/VSD, complete transposition of the great arteries with associated ventricular septal defect; CAVSD, complete atrioventricular septal defect.

tricular septal defects with concomitant inspection of the defect, and a further five patients have had pulmonary artery banding as an initial procedure.

METHODS

Echocardiographic studies were performed in the standard manner as described in our work on the imaging of isolated ventricular septal defects.[9] Cross sectional images were obtained with an ATL Ultramark IV mechanical sector scanner with 5·0 and 7·5 MHz transducers, to achieve high resolution images. Conventional Doppler (both pulsed and continuous wave) and colour flow imaging studies were then obtained by a Toshiba SSH 65 A with 2·5, 3·7, and 5·0 MHz phased array transducers. Colour flow studies were performed in both the power and the variance modes with appropriate gain and filter settings. The diagnosis by colour flow imaging of a single ventricular septal defect was considered definitive when colour flow (either turbulent or laminar) was shown traversing the interventricular septum. Where no transseptal flow was visualised the presence of a restrictive defect was inferred if a high velocity or turbulent jet was identified exiting from the right ventricular aspect of the septum into the right ventricular cavity. In restrictive defects the transseptal and right ventricular flow disturbance when visualised was invariably high velocity and turbulent, so a mosaic pattern was seen on the variance colour flow map (fig 1). In non-restrictive defects transseptal systolic flow was invariably of relatively low velocity and laminar (fig 2) with no turbulence being colour encoded. Transseptal flow within the multiple defects was therefore frequently best depicted by colour flow imaging in the power mode. Colour M mode studies, in the velocity mode, were also performed in non-restrictive defects because in theory systolic flow acceleration could occur either within the defect(s) or at the right ventricle exit point without turbulence being present (fig 3). The inherently higher sampling rate of colour M mode should make this method more sensitive

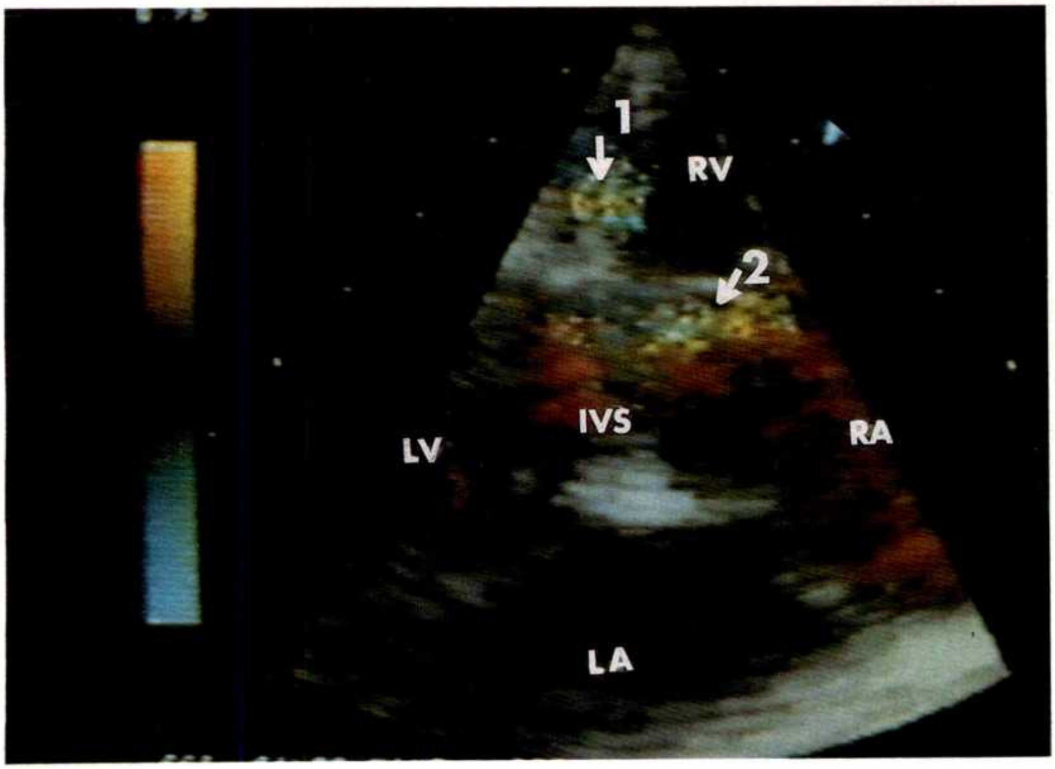

Fig 1 *A modified four chamber view with the transducer angled towards the short axis view and recorded during systole in a patient with multiple restrictive ventricular septal defects. There are two mosaic jets exiting from the right ventricular aspect of the interventricular septum (arrows 1 and 2). In this view, the mosaic colour flow pattern completely traverses the septum only through the perimembranous defect (arrow 2). The midtrabecular defect (arrow 1) is depicted by a mosaic jet exiting from the right ventricular aspect of the septum. LV, left ventricle; RV, right ventricle; LA, left atrium; RA, right atrium; IVS, interventricular septum.*

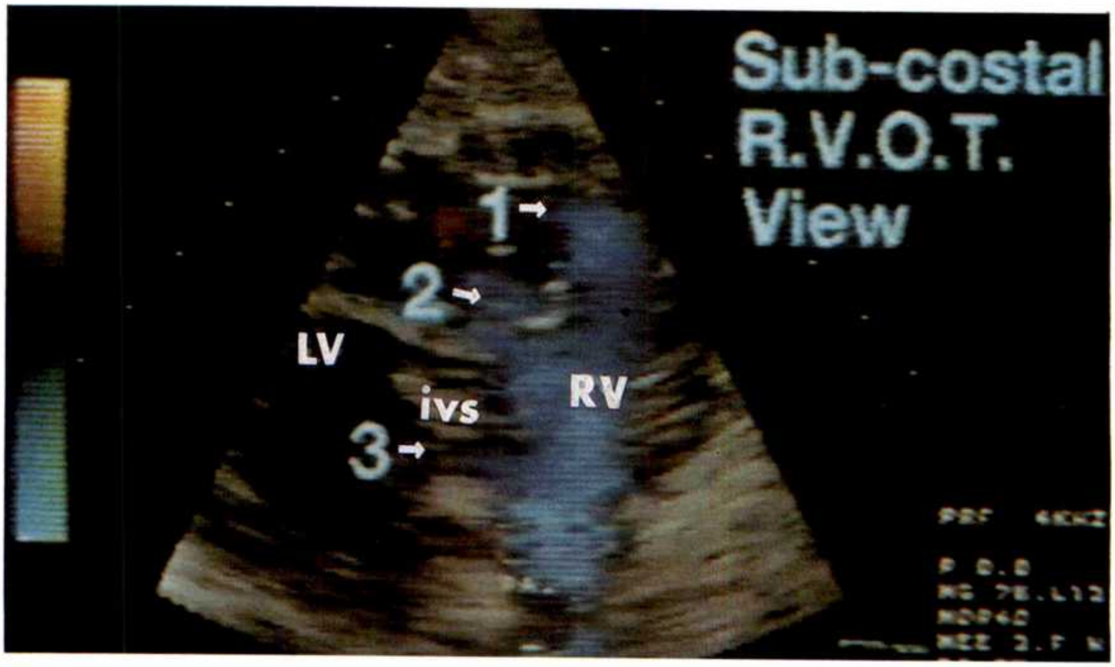

Fig 2 *A subcostal view of the right ventricular outflow tract recorded during systole in a patient with multiple non-restrictive ventricular septal defects. Only low velocity laminar flow (blue) with no evidence of flow acceleration traverses the interventricular septum at the three points at which the ventricular septal defects were present (arrows 1, 2, and 3). There is no aliasing or turbulence within the septum or the right ventricle. See legend to fig 1 for abbreviations.*

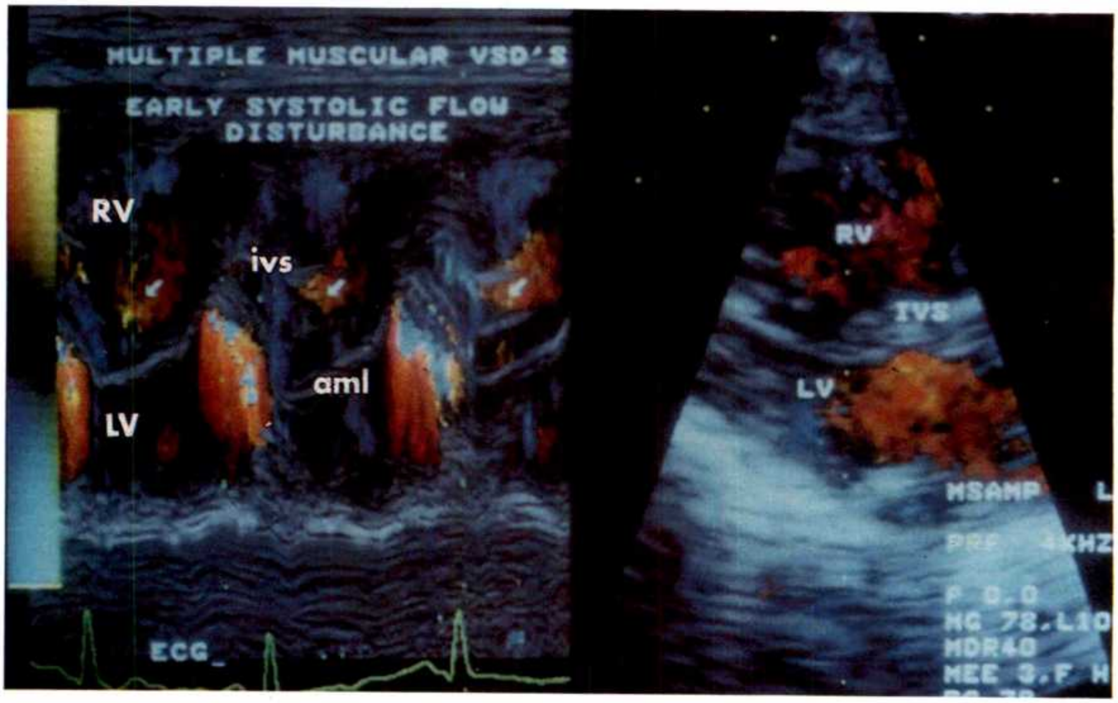

Fig 3 *A colour flow map and colour M mode recorded in the parasternal long axis view from a patient with non-restrictive multiple muscular ventricular septal defects and an appreciable left to right shunt. The colour flow map on the right is frozen in late systole; there is no turbulence within the septum or the right ventricle. In the colour M mode on the left high velocity turbulent diastolic flow entering the left ventricular inflow was caused by high transmitral flow. In early systole there is colour flow traversing the interventricular septum and entering the right ventricle (arrows). The transseptal colour flow shows a colour shift from red to yellow indicating flow acceleration without turbulence or aliasing. See text for further details. aml, anterior mitral valve leaflet. See legend to fig 1 for other abbreviations.*

than colour flow imaging alone and thus could be a useful adjunct in the definition of multiple ventricular septal defects by detecting multiple discrete areas of acceleration of transseptal or right ventricular flow.

All cardiac catheterisation studies were performed under general anaesthesia with pressure recordings being taken before angiography. Left ventriculography was performed in the appropriate angled axial projections as described by Soto *et al.*[13] Right ventriculography was also performed in all patients except those with isolated ventricular septal defects.

Although both echocardiographic and angiographic studies were sometimes performed by the same cardiologist in the same patient, all results were later assessed by one or more experienced independent observers.

Because these patients entered into the study in various ways it was not always possible to perform simultaneous angiographic and ultrasound studies. But both types of study were always performed within 24 hours of each other.

The results obtained were initially analysed as a total patient group and then further analysed after being subdivided into groups with restrictive or non-restrictive defects. Non-restrictive defects were defined as showing equal peak systolic pressures in both ventricles measured by cardiac catheterisation. Patients with restrictive multiple ventricular septal defects had a peak systolic pressure in the left ventricle that exceeded that in the right ventricle, except patients with transposition of the great arteries in whom the systemic ventricle was on the right.

Results

Cross sectional echocardiography showed at least one ventricular septal defect in all 31 patients and one or more further defects in 12 (38%) patients; there was no difference in the detection rate of multiple defects between the groups with restrictive (39%) and non-restrictive defects (38%) respectively (table 2). The diagnosis of multiple ventricular septal defects based on cross sectional imaging was subsequently confirmed in all 12 patients by a combination of either colour flow imaging, ventriculography, or operation or all three. In this series the addition of conventional pulsed and continuous wave Doppler to the cross sectional imaging information did not increase the detection of multiple ventricular septal defects. The conventional Doppler methods were useful for distinguishing between patients with restrictive or non-restrictive haemodynamic function. In contrast, colour flow imaging alone, by visualising multiple areas of transseptal flow detected the presence of two or more ventricular septal defects in 24 (77%) of the 31 patients studied. When these were subdivided into groups with restrictive and non-restrictive defects, colour flow imaging had a much higher diagnostic accuracy in the restrictive group (89%) than in the non-restrictive groups (62%). The diagnosis was confirmed in all 24 patients by either ventriculography or operation or both. A comparison of the different colour flow patterns obtained showed that there was no difficulty in distinguishing between restrictive (turbulent mosaic pattern) and non-restrictive (non-turbulent laminar flow pattern) defects. In patients with equal peak systolic ventricular pressures the detection of multiple ventricular septal defects depended on the ability to visualise colour encoded transseptal flow. The predominant direction of any shunt did not affect this ability but simply altered the colour of the transseptal flow (flow towards the transducer was encoded as red and flow away was encoded as blue).

Table 2 *Diagnostic accuracy of non-invasive and invasive techniques*

	Cross sectional alone No (%)	*CFM No (%)*	*LV angio No (%)*
Restrictive defects (n = 18)	7 (39)	16 (89)	15 (83)
Non-restrictive defects (n = 13)	5 (38)	8 (62)	5 (38)
Total (n = 31)	12 (39)	24 (77)	20 (65)

CFM, colour flow mapping, LV angio, left ventricular cineangiography.

Colour M mode studies showed transseptal flow in the largest defect in patients with non-restrictive ventricular septal defects, but could not confirm the diagnosis of multiple defects in any case. Transseptal flow was usually laminar but in one patient systolic flow acceleration was detected. This systolic flow acceleration was indicated by a change in colour intensity while flow itself remained laminar (fig 3). This pattern of flow acceleration correctly predicted the presence of equal systolic ventricular pressures and a significant left to right shunt (confirmed at catheterisation). All other patients with multiple non-restrictive defects had bidirectional shunting.

Left ventriculography showed multiple ventricular septal defects in only 20 (65%) of the 31 patients. The diagnostic accuracy of ventriculography was 83% for restrictive defects and 38% for non-restrictive defects.

Discussion

The results of this study confirm that colour flow imaging is a useful adjunct in the non-invasive diagnosis of multiple ventricular septal defects. It proved to be better than cross sectional imaging alone, and we found that the addition of the conventional Doppler methods did not increase the diagnostic yield. Our results for the overall diagnostic accuracy of cross sectional imaging alone (39%) and colour flow imaging (77%) for multiple ventricular septal defects are similar to those previously reported by Ludomirsky and coworkers who showed an overall diagnostic sensitivity for cross sectional imaging and colour flow imaging of 38% and 72% respectively.[11] When we subdivided our patients into groups with restrictive and non-restrictive defects, however, colour flow imaging was found to have a higher sensitivity for the diagnosis of multiple restrictive defects (89%) than for multiple non-restrictive defects (62%). This lower sensitivity for non-restrictive defects seems to be a function of the absence of turbulent transseptal flow, which is a consequence of the equal peak systolic ventricular pressures. This was the fundamental difference between restrictive and non-restrictive defects as shown by colour flow imaging—turbulent high velocity flow encoded as a mosaic pattern was easier to visualise than low velocity laminar flow.

Diagnosis in the non-restrictive group was more difficult when a large ventricular septal defect (usually perimembranous) was found in combination with one or more small muscular defects; our study showed that under these circumstances colour flow information may only be visualised within the largest defect with no colour flow appearing in the small defect(s). This phenomenon was seen with both the velocity and power display modes. Whether this represented a true lack of flow in the smaller defects or was an artefact induced by either the analysis algorithm of the equipment or a failure to align correctly with defect flow is not clear, but if this is a true finding and flow can occur only over one of the multiple defects present, then it would in part explain the relatively high incidence of false negative diagnoses when colour flow imaging is used to identify multiple non-restrictive defects. The inherent higher sampling rate of colour M mode might in theory detect transseptal flow in these small additional defects that were missed by colour flow mapping. In practical terms, however, this was not the case because colour M mode only detected transseptal flow in the largest defect present.

The combination of isolated small multiple ventricular septal defects and pulmonary stenosis (or pulmonary band) might make diagnosis difficult, although this particular anatomical arrangement was not encountered in this series. Such an arrangement causes non-restrictive haemodynamic function and equal peak systolic ventricular pressures, but if the pulmonary obstruction were to be removed then the defects would be restrictive (because they are small) and might therefore not require concomitant closure. The data described above suggest that such multiple small defects will not be reliably visualised by colour flow imaging.

There were other difficulties with colour flow imaging, both in the groups with restrictive and non-restrictive defects when multiple ventricular septal defects lay close together. The limitation of lateral resolution inherent in the technique do not allow the separation of turbulent jets that lie within $<0{\cdot}5$ cm of each other. In contrast, the combination of restrictive perimembranous and apical trabecular defects was accurately defined because the turbulent jets were well separated and there was no difficulty with lateral resolution. Also the detection of multiple defects in the outlet muscular septum (either restrictive or non-restrictive) will always prove difficult both because of the difficulties in imaging this region and the subsequent difficulties with lateral resolution with colour flow imaging. We believe that these are the reasons for the diagnostic failures in this study.

The overall diagnostic accuracy of left ventriculography for multiple ventricular septal defects reported in this study (65%) is lower than that reported by Fellows and coworkers (86%).[5] There are probably two reasons for this. Firstly, the proportion of restrictive defects in their study group was much higher—so the diagnostic accuracy of restrictive defects in our study (83%) is a more appropriate comparison and does accord with their findings. Secondly, their study was not primarily designed to assess the diagnostic accuracy of their technique and it is possible that some cases that were missed by left ventriculography were not confirmed by surgical inspection (that is where a palliative procedure such as a pulmonary artery band or a systemic-pulmonary shunt was performed rather than a total correction). This would be particularly applicable to patients with non-restrictive defects in whom the diagnosis by left ventriculography in this study was especially poor (38%).

The relative diagnostic accuracy of colour flow imaging (89%) and left ventriculography (83%) for all types of multiple restrictive ventricular septal defects in our study was similar. There were no cases in this subgroup that were diagnosed by left ventriculography but not by colour flow imaging. So left ventriculography was of no additional benefit in patients in this study with multiple restrictive defects. In patients with multiple non-restrictive defects, the results were different; in this subgroup there were two patients in whom the diagnosis was made by left ventriculography but was missed by colour flow imaging. So although the diagnostic accuracy for colour flow imaging (65%) was much higher than that of left ventriculography (38%), the overall diagnostic accuracy for multiple non-restrictive ventricular septal defects was highest when the information from the two techniques was used together (77%).

None the less, 23% of multiple non-restrictive defects were misdiagnosed as single isolated ventricular septal defects. We feel that this is a fair reflection on the complexity of the diagnosis presented by such defects. It is our opinion that the diagnostic yield will be only slightly increased with more experience in the use of the diagnostic techniques described above and that up to one in five of multiple non-restrictive defects and one in 10 of multiple restrictive defects may be missed.

We conclude that colour flow imaging was the single most accurate diagnostic technique for the prediction of multiple restrictive ventricular septal defects. Whereas the diagnosis of multiple non-restrictive defects was best achieved in this study when colour flow imaging and left ventriculography were used together, even the combined approach missed a considerable number of patients with multiple ventricular septal defects.

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Assessment of the orifice diameter by a multigated pulsed Doppler system in children with congenital semilunar valve stenosis

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SUMMARY This study investigated whether the jet diameter measured by a multigated pulsed Doppler system could be used to assess the severity of valve disease in children with pulmonary ($n = 11$) or aortic ($n = 4$) valve stenosis. The results obtained were compared with those obtained at cineangiography and at operation. Multigated pulsed Doppler examination of a stenosed valve showed a region of relatively high velocities in the velocity profile (jet flow). There was good agreement between the diameter of the disturbed region on the Doppler echocardiogram and the diameter of the jet on the lateral angiocardiogram. In severe valve stenosis the agreement between the valve diameters measured by multigated pulsed Doppler and at operation was also good. In less severe valve stenosis Doppler measurements systematically underestimated the valve diameter at operation. It is likely that the functional opening of a semilunar valve is a more relevant estimate of the degree of stenosis than the anatomical measurement of the orifice.

The findings of this study indicate that multigated pulsed Doppler systems are useful in the non-invasive diagnosis of stenotic valve disease.

The severity of valve stenosis is usually assessed by the pressure gradient across the valve[1 2] or from the orifice area (calculated by the Gorlin formula[3]). The orifice area can also be derived from the width of a jet of contrast.[4] This angiocardiographic orifice area accorded with the haemodynamically calculated orifice area, when the area of the stenosis was assumed to be circular.[4] In eight out of nine patients the valve orifice calculated from the angiocardiographic jet diameter was smaller than the diameter measured during operation.[5]

The introduction of echocardiography, especially cross sectional and Doppler techniques, has improved the potential for the non-invasive prediction of the severity of valve stenosis.[6] Pulsed and continuous wave Doppler systems allow the gradient across a stenotic valve to be calculated from the Bernoulli equation.[7–9] But this approach is restricted by the dependence of the pressure gradient on cardiac output. Also single gated pulsed Doppler systems cannot accurately detect high blood flow velocities. So single gated pulsed Doppler is reliable only in mild pulmonary valve stenosis.[10]

Johnson *et al* used a single gated pulsed Doppler device to detect the jet in aortic valve stenosis.[11] They measured the diameter of the jet by assessing the width of a region of flow disturbance distal to the stenosis. But this technique was accurate only when stenosis was severe. Recently, Veyrat *et al* introduced a single gated pulsed Doppler mapping technique to assess the severity of aortic valve stenosis in adults.[12] The method reliably diagnosed less severe aortic valve stenosis, but it was time consuming.

Multigated pulsed Doppler systems allow the on-line recording of series of velocity profiles at discrete time intervals during a cardiac cycle.[13–15] Under normal circumstances the systolic velocity profiles in the pulmonary artery and ascending aorta are likely to be nearly flat, but valve stenosis produces a region of relative high flow velocities (a jet).

We have assessed the accuracy of a multigated pulsed Doppler system used to measure orifice size

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non-invasively. The multigated method is less dependent on cardiac output than the single gated method.

Patients and methods

PATIENTS

For 28 months all children with pulmonary valve or aortic valve stenosis undergoing catheterisation and subsequent cardiac surgery were admitted to the study if satisfactory cross sectional and Doppler echocardiograms were obtained with a 5 MHz system and it was possible to perform a multigated pulsed Doppler investigation. The investigation was part of the routine examination before heart catheterisation and operation.

Eleven children had isolated pulmonary valve stenosis. The age at catheterisation ranged from 14 days to 3 years 8 months except for one patient with Noonan's syndrome,[16] who was 11 years 8 months. The second group consisted of four children with aortic valve stenosis, aged from 13 days to 1 year 2 months at catheterisation.

In those with pulmonary stenosis the delay between catheterisation and operation was about two months (range 13 days to 4 months 3 weeks). In two children (cases 1 and 5, table 1) the delay was 23 and 20 months. In all those with pulmonary stenosis all multigated pulsed Doppler examinations were performed a few days before operation, under sedation if necessary.

The mean interval between the multigated pulsed Doppler examination and catheterisation or operation was 10 days (range 1–30 days) in those with aortic valve stenosis.

CATHETERISATION STUDIES

All children were investigated by catheterisation except for one patient with pulmonary valve stenosis. She had an operation on the basis of echocardiographic and Doppler investigations alone.

Catheterisation was performed under general anaesthesia with artificial ventilation. Pressures were measured under steady state conditions; when it was possible to pass the stenosis we measured the gradient across the stenosed valve.

The ratio of right (RV) to left ventricular systolic pressure (LV) was used to estimate the severity of the stenosis in patients with pulmonary valve stenosis (modification after Emmanouilides and Baylen[1]). To avoid the effects of infundibular stenosis we measured the pressure in the right ventricular outflow tract and not in the cavity. Severe pulmonary valve stenosis was defined as a RV/LV ratio ≥1·00 and a moderate stenosis as a RV/LV ratio between 0·5 and 1·00.

When the left ventricle could not be reached at catheterisation we measured the systolic brachial

Table 1 *Orifice diameters in pulmonary valve and aortic valve stenosis measured by multigated pulsed Doppler (MPD), cineangiocardiography, and at operation. The reference standards for age and height are derived from Schulz and Giordano.*[19]

		Pulmonary valve stenosis				
		Before operation			*At operation*	
Patient number	*RV/LV systolic pressure ratio*	*MPD diameter (mm)*	*Angio jet diameter (mm)*	*Reference diameter (mm)*	*Operation diameter (mm)*	*Reference diameter (mm)*
1	0·53	4·9	4·9	13·7	12	14·7
2	0·57	6·3	5·2	10·4	11	10·6
3	0·64	4·4	3·7	14·3	11	14·3
4	0·69	7·3	6·5	15·7	12	16·3
5	0·70	—	7·0	13·2	9	14·1
6	0·70	3·1	3·5	10·1	6	10·2
7	1·00	5·8	5·1	12·6	6	12·7
8	1·14	5·5	5·2	14·1	5	14·2
9	1·17	4·2	No jet	7·2	4	8·6
10	1·60	4·1	3·0	7·3	3	9·2
11	—	7·3	—	11·0	6	11·0
		Aortic valve stenosis				
		Before operation			*At operation*	
Patient number	*LV-AO gradient in mm Hg*	*MPD diameter (mm)*	*Angio jet diameter (mm)*	*Reference diameter (mm)*	*Operation diameter (mm)*	*Reference diameter (mm)*
12	50	3·8	3·8	6·8	4	6·8
13	75	3·9	3·7	8·7	3	8·7
14	45	3·8	3·8	7·3	3	8·3
15	95	3·6	3·4	8·3	3	8·3

RV, right ventricle; LV, left ventricle; AO, aorta.

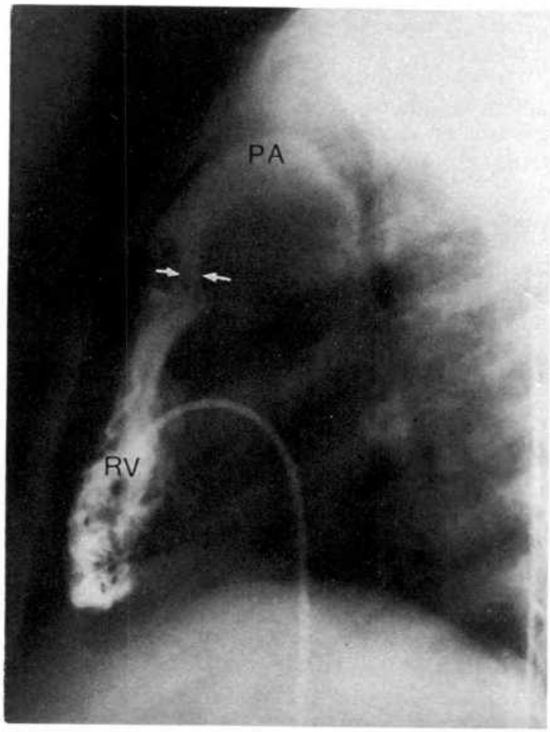

Fig 1 *Lateral cineangiocardiographic view of the jet in pulmonary valve stenosis after contrast injection into the right ventricle. The diameter of the jet is measured just downstream from the stenotic valve. The site of measurement is indicated with two arrows. RV, right ventricle; PA, pulmonary artery.*

artery pressure by an appropriate cuff, using a Dynamap blood pressure measuring system. This systemic arterial pressure was then used to assess the RV/LV ratio.

In infants aortic valve stenosis was regarded as severe when the peak systolic gradient across the valve was ≥50 mm Hg. In critical aortic valve stenosis, however, the pressure in the left ventricle and the gradient across the valve may be lower because left ventricular function is impaired; this will lead to an underestimation of the severity of the disease.

CINEANGIOCARDIOGRAPHY

Cineangiocardiography was performed during catheterisation to visualise the jet stream. A lateral view was used in those with pulmonary valve stenosis and a left anterior oblique view in those with aortic valve stenosis. The contrast medium was Angiografin 65% (meglumine-amidotrizoate) in a dose of 0·5–2 mg/kg body weight. The contrast medium was injected into the cavity of the ventricle with a catheter dependent flow rate (NIH 5–7 F). The cine frame rate was 75/s (fig 1).

From each film we selected a frame showing a well defined opacified jet and we measured the diameter of the jet stream. This procedure was performed three times with an interval of at least one day between the measurements. The site of measurement was just downstream of the stenotic valve. In most cases the jet flow was detected in early systole of the first or second heart beat after contrast injection. We used the diameter of the image of the catheter in the right ventricular outflow tract as a reference to calculate the real jet diameters. We took the mean of a series of three measurements as the diagnostic value.

MULTIGATED PULSED DOPPLER MEASUREMENTS

We used a 5 MHz multigated pulsed Doppler system with 64 adjacent sample volumes over a distance of 38·4 mm (one sample volume = 0·6 mm in length). To visualise the site of investigation, we connected the multigated pulsed Doppler system to an ATL mark V real time echo-scanner. The site of sampling across the vessel was selected by moving the M line direction and adapting the delay indicating the depth of the sample range along the M line just as in the single gated pulsed Doppler system.

Measurements were made with child lying on its left side. To visualise the pulmonary artery or the ascending aorta in a long axis view, we placed the transducer in the first or second left intercostal space in patients with pulmonary valve stenosis and in the third or fourth intercostal space in patients with aortic stenosis. If necessary the patients were sedated with an intramuscular injection of promethazine (0·5 mg/kg), chlorpromazine (0·5 mg/kg), and pethidine (1 mg/kg).

The flow velocity profiles of the orifice were recorded with the M line positioned just downstream from the stenotic valve.[17,18] The angle of the M line to the axis of the pulmonary artery was measured on the sector scan. To calculate the jet diameter we assumed that the flow direction corresponded with the axis of the pulmonary artery. To obtain a cross sectional profile we chose an angle of about 80°; at 90° the Doppler signal becomes impaired. Narrowing of the valve orifice caused a region of high velocities in the profile. The diameter of this region in systole was assumed to represent the flow diameter of the orifice. Aliasing was seen if the jet flow exceeded the velocity limits of the pulsed mode. When this happened we increased the angle of interrogation. An observation close to 90° with the jet will affect the accuracy with which the jet diameter can be established since the velocities, corrected for the estimated angle, are compared with a threshold. With a pulse repetition frequency of 7·8 KHz, velocities of up to 60 cm/s can

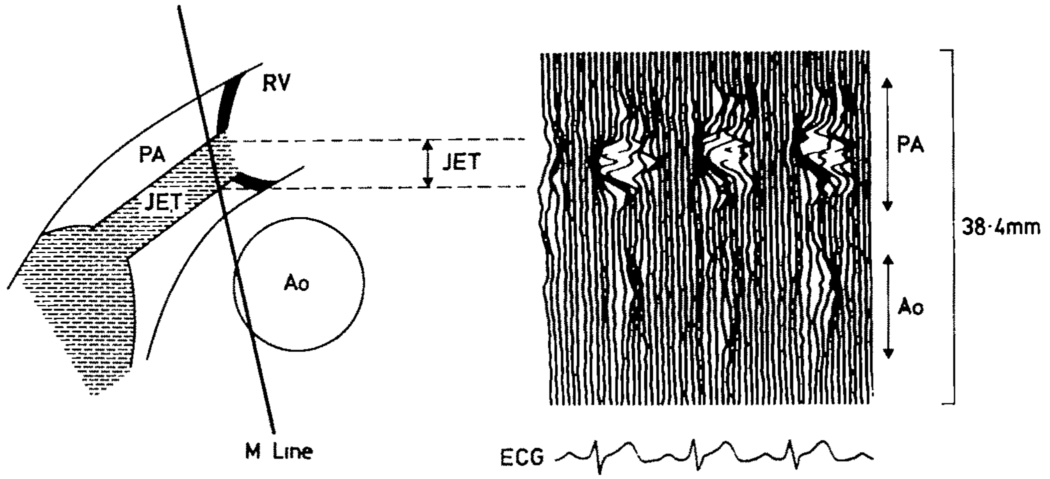

Fig 2 *Example of a pulmonary valve stenosis investigated with multigated pulsed Doppler. The site of measurement (M line) is indicated. There are three measurable orifice flow profiles in the pulmonary artery (PA). In systole in the first flow profile the diameter of the ostium flow is indicated ("JET"). It runs from the beginning of the first fast deflection till the end of this deflection. The jet diameter is related to the total length of the 64 sample gates (38·4 mm) and corrected for the angle between the flow direction and M line. There are vague aortic (Ao) flow patterns below the pulmonary artery flow profiles. The electrocardiogram is shown as a time scale.*

be estimated at 0°, up to 3·5 m/s at 80°, and up to 7·0 m/s at 85°. Deviations from the real jet direction (for instance 90°) and assumed jet direction (for instance 70°) are not critical because a deviation of 20° gives rise to a maximum error of 12%. The number of contributing gates (0·6 mm each) gave the diameter of the jet flow, which was corrected for the estimated angle of interrogation (fig 2). A series of frames of velocity profiles was stored and only the largest and most typical jet flow patterns were chosen because the smaller disturbances will have been measured obliquely. Measurements were repeated three times and the mean of these measurements was used for further analysis.

MEASUREMENTS DURING OPERATION

During operation the diameter of the pulmonary valve orifice was measured with a circular probe before valvotomy or valvectomy. The probe that just fitted the valve without stretching it was regarded as the size. To avoid accidental rupture of stenosed aortic valves we measured the length of the slit of the collapsed valve, which we assumed to be half the internal circumference of the orifice. This approach was necessary because the clinical consequences of aortic valve regurgitation are severe. These calculated measurements were rounded down to probe values. In one patient (case 12) the diameter was measured at necropsy.

We used the age and height dependent internal circumference reference values[19] to calculate the valve orifice.

S de K measured the width of the jet by the multigated pulsed Doppler system and by angiocardiography. The surgeon was not informed of the outcome of the non-invasive measurements.

STATISTICAL ANALYSIS

The mean (2 SD) of paired differences was calculated to compare the results of multigated pulsed Doppler and cineangiocardiography. To compare the results of multigated pulsed Doppler and operation we calculated the mean (2 SD) for only the severe stenoses. All the results are presented (figs 3 and 4) with limits of agreement according to Bland and Altman[20] and Gardner and Altman.[21]

Results

The 1 SD of the mean of each series of three measurements ranged from 0·05 to 0·44 mm at angiocardiography and from 0·15 to 0·83 mm in the multigated pulsed Doppler measurements (one sample gate measures 0·6 mm).

Table 1 lists the results. In patient 5 the multigated pulsed Doppler investigation was impossible because the child would not stay still. Patients 4 and 9 had

Noonan's syndrome and in one of them no jet was detected. One patient (case 11) had cardiac operation without catheterisation; the reference diameter at operation suggested severe pulmonary stenosis (orifice area <30% of normal (table 1). The valves were tricuspid (shape unknown in patient 6) in those with pulmonary stenosis and bicuspid in those with aortic stenosis.

Table 2 shows the mean (1 SD) of the paired differences of the different methods of investigation. There was strong agreement between the jet diameters assessed by the multigated pulsed Doppler system and angiocardiography. Figure 3 shows the combined results for the groups with pulmonary and aortic valve stenosis. The paired difference between the diameters measured by multigated pulsed Doppler and angiocardiography were compared with the mean diameter calculated from multigated pulsed Doppler and angiographic findings.

Figure 4 shows a comparison of the paired differences between the diameters assessed by multigated pulsed Doppler and at operation and the mean diameter derived from the findings at multigated pulsed Doppler and operation. The mean and 2 SD are calculated only for the severe pulmonary and aortic valve stenoses. The values of moderate pulmonary valve stenosis were outside these limits of agreement (2 SD), but agreement between the methods was good in patients with severe stenosis. The multigated pulsed Doppler method underestimated the diameter of moderately stenosed valves measured at operation, but only to the same extent as cineangiocardiography did.

Discussion

We found that, whatever the degree of stenosis, the jet diameter measured on the angiocardiogram corresponds well with the diameter measured by multigated pulsed Doppler. The diameter assessed from the width of the jets correlated well with the diameter measured at operation when pulmonary or aortic valve stenosis was severe. When the stenosis was less severe, however, the diameter from the jet systematically underestimated the diameter measured at operation.

Table 2 *Comparison of diameters*

(a) Diameters in all pulmonary and aortic valve stenoses			
Variable	*No*	*Mean (mm)*	*1 SD*
Multigated minus angio	12	0·40	0·46
Multigated minus operation	15	−1·44	2·96
Angio minus operation	13	−2·25	3·08
(b) Diameters in severe pulmonary and aortic valve stenoses			
Variable	*No*	*Mean (mm)*	*1 SD*
Multigated minus angio	7	0·38	0·39
Multigated minus operation	9	0·57	0·53
Angio minus operation	7	0·13	0·57

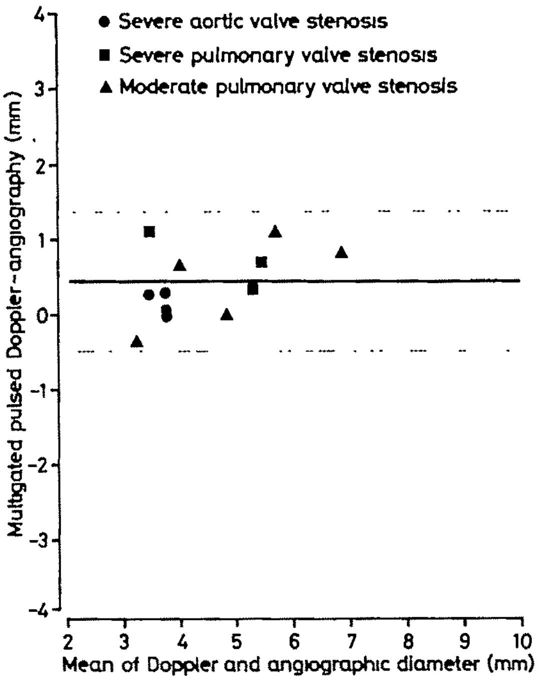

Fig 3 *Patients with pulmonary or aortic valve stenosis. Differences between the diameters assessed with the multigated pulsed Doppler system and at cineangiocardiography are shown as a function of the mean diameters calculated from the findings with both methods. The mean (solid line) and ±2 SD (dotted lines) are indicated.*

Multigated pulsed Doppler and angiography both measure functional diameter. With multigated pulsed Doppler systems a local disturbance in the flow profile can be visualised, and on the angiogram a region of fast filling contrast is seen. With multigated pulsed Doppler systems the frontal-dorsal diameter is assessed. The lateral projection at cineangiocardiography also estimates the frontal-dorsal diameter. In aortic valve stenosis a left oblique view is used, with nearly the same diameter in cross section as in multigated pulsed Doppler. The jet is directed towards the anterior wall of the main pulmonary artery (fig 1). The multigated pulsed Doppler measurements are performed at an angle of interrogation close to 90°. Underestimation of the orifice diameter by the multigated technique when the stenosis is less severe accords with previous observations.[5 22] Compression of the jet by areas of recirculation[23] is not likely to be responsible for the

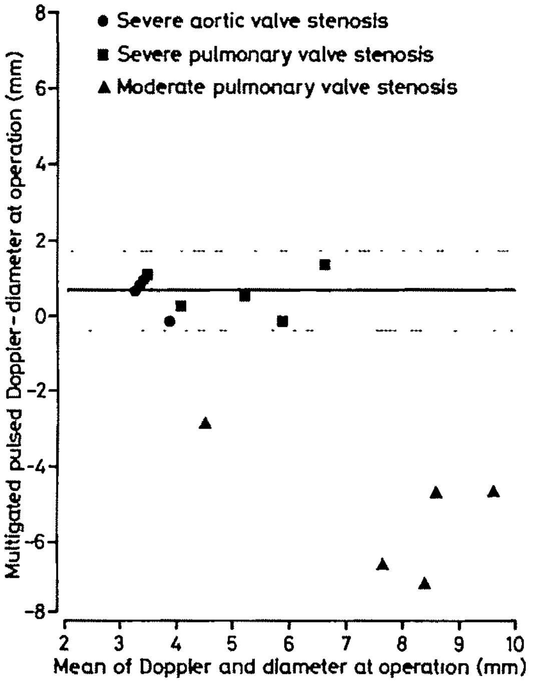

Fig 4 *Patients with pulmonary or aortic valve stenosis. Differences between the diameters assessed with the multigated pulsed Doppler system and at operation are shown as a function of the mean diameters calculated from the findings with both methods. The mean (solid line) and ± 2 SD (dotted lines) of the severe pulmonary and aortic valve stenosis are indicated.*

underestimation of the diameter.[24] The most likely explanation for the discrepancy is the difference between functional opening and the anatomical orifice assessed at operation. Under normal circumstances and in slight to moderate valve diseases maximum valve opening is not needed for adequate outflow at rest. The probe method probably measures the largest possible circular aperture. In severe stenosis although the orifice reaches its largest possible diameter blood flow is obstructed. In this situation the diameter measured at operation is likely to be similar to the functional diameter because the orifice can only be passed by a probe with a diameter about equal to the maximum diameter of the valve orifice.

The idea that the valve diameter calculated from the width of the jet represents the functional diameter is supported by the fact that the jet diameter assessed by cineangiocardiography and the jet diameter calculated by the Gorlin equation are usually similar.[4,5] Berman *et al* only reported on cineangiograms obtained in a lateral view.[4] The assumption that the orifice is circular seems to be valid in more severe congenital pulmonary valve stenosis.[25-28] When valve malformation is severe this assumption is not valid. These cases, however, can easily be diagnosed by cross sectional echocardiography. In one angiographic study the valve area was smaller than that calculated by the Gorlin equation.[22] In this study, however, oxygen consumption (used to calculate cardiac output) was assumed rather than measured and this may introduce errors in the calculated haemodynamic area.

Nevertheless, in patients with moderate to severe aortic stenosis the diameter of the orifice measured by single gated pulsed Doppler flow mapping techniques resembled the diameter assessed haemodynamically.[11] Although Veyrat *et al* warned that the orifice of the aortic valve may not be circular,[12] 56% of the orifices were circular and only 6% were slits. These findings support the idea that functional assessment of the degree of stenosis is better than anatomical measurements.

With the new techniques of colour coded Doppler the jet is directly visible. Diameter measurements, however, depend on the adjustment of the colour imager. The combination of detection of jet direction by colour Doppler and measurement of the diameter by multigated pulsed Doppler seems promising.

In conclusion, a jet diameter that corresponds to that measured on the angiocardiogram can be measured non-invasively by multigated pulsed Doppler systems. This diameter probably represents the functional opening of the valve.

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Case reports

Venospastic phenomena of saphenous vein bypass grafts: possible causes for unexplained postoperative recurrence of angina or early or late occlusion of vein bypass grafts

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SUMMARY Angina recurred in a 54 year old white man after multivessel coronary artery bypass surgery. Fourteen months after operation the frequency and intensity of his mixed angina increased and cardiac stress testing was positive. Repeat cardiac catheterisation showed that all the bypass grafts were widely patent; however, spasms of a vein graft to right coronary artery system were clearly seen. Treatment with calcium blocking agents and long acting nitrates abolished the symptoms during 16 months of clinical follow up.

Coronary artery vasospasm is seen in about 3% of patients undergoing coronary arteriography[1] and interest in this entity is growing.[2] Spasm may occur in normal vessels and those that are mildly or severely diseased and in patients with no symptoms or with severe disabling angina at rest.

Spasm was seen during and soon after operation in aortocoronary vein bypass grafts in two cases.[3,4] To our knowledge confirmed, symptomatic, late, and chronic saphenous vein bypass graft venospasm has not been described before. In this report we present an interesting and rather unusual case of spasm in an aortocoronary vein bypass graft in a patient in whom mixed angina (pain at rest and during effort in the left shoulder and left neck) developed postoperatively with intensification of symptoms about 14 months after coronary artery bypass operation.

Case report

A 54 year old white man underwent coronary artery bypass surgery on 10 January 1983, because of considerable angina and positive stress testing. He received a left internal mammary artery anastomosis to the left anterior descending artery, a vein bypass graft to the first major diagonal division, a sequential vein graft side-to-side to the second marginal and end-to-side to the third marginal division of the circumflex system, and an additional sequential vein graft, side-to-side to the posterior descending branch and end-to-side to the distal right branch of the right coronary artery system.

His intraoperative and immediate postoperative course was uneventful. He remained free of symptoms except for occasional episodes of vague discomfort in the left shoulder and chest that was often unrelated to effort.

In March 1984 he began to experience increasing episodes of pain in the left shoulder and left neck at rest and on mild physical effort. In July 1984, while at work, he experienced three episodes of pain in the left neck and shoulder with radiation to the upper left arm and two episodes of a feeling of pressure under the lower sternum and numbness and tingling of the fingers of the left hand. These episodes occurred

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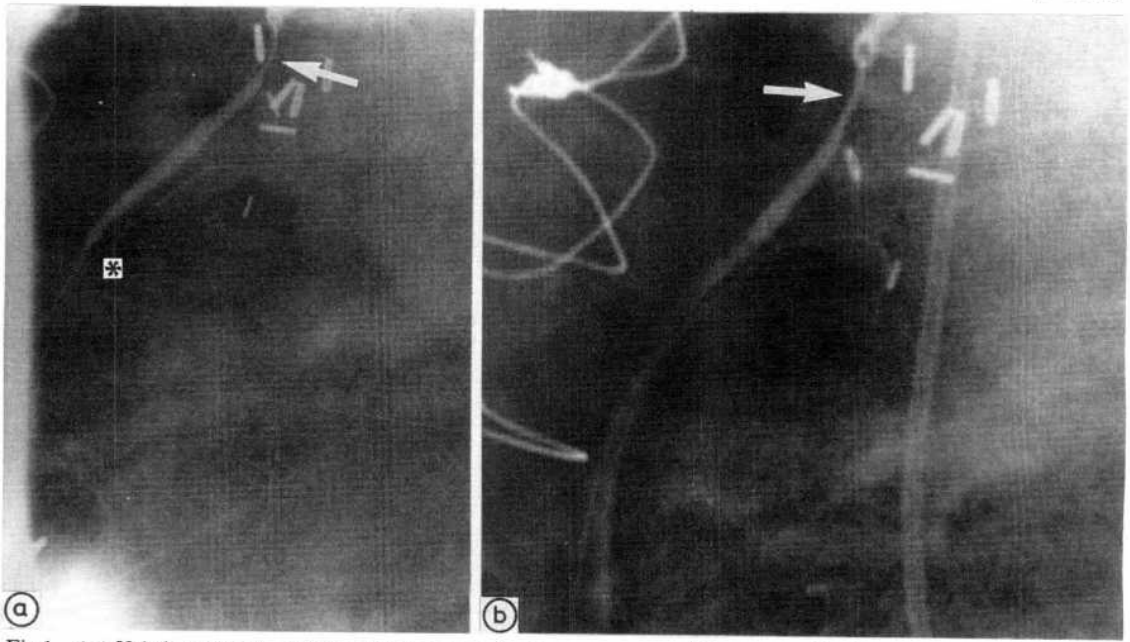

Fig 1 *(a) Vein bypass graft to right coronary artery showing severe spasm of its most proximal segment (arrowed) and slow distal run off (asterisk). (b) Vein bypass graft to right coronary artery system during subsequent cardiac catheterisation showing further proximal vein graft spasm (arrow).*

during his usual daily walking activities at his supervisory job. During one episode he became sweaty and dizzy.

He was seen in the emergency room but there was no evidence of myocardial infarction or ischaemia. Cardiac stress testing caused the development of pain in the left shoulder and left neck and extrasystoles at 9·6 metabolic equivalents without associated typical ischaemic changes in the ST segment.

Repeat cardiac catheterisation and coronary angiography on 10 July 1984 showed widely patent vein bypass grafts to the marginal divisions of the circumflex coronary artery and to the diagonal branch of the left anterior descending coronary artery as well as a patent left internal mammary artery graft to the left anterior descending vessel. There was no evidence of progression of atherosclerosis in the native left coronary artery system.

In the sequential vein graft to right coronary artery system there was a 95% segmental stenosis in the 1·5 cm most proximal segment with very slow filling of the distal segment of this vein graft (Fig 1a). In addition, the side-to-side arm of this vein graft anastomosis to the posterior descending branch of the right coronary artery was totally occluded. The end-to-side anastomosis to a large distal right branch of the right coronary artery, however, was widely patent with good anterograde visualisation of this native vessel. The posterior descending branch of the right coronary artery was also well visualised on anterograde injection of contrast into the native right coronary artery, which showed about 40–50% stenosis in its midsegment and total occlusion of the distal right branch at its origin just before the end-to-side anastomosis of its respective vein graft.

The patient was then considered for percutaneous transluminal angioplasty of the proximal portion of the vein graft to this large distal right branch of the right coronary artery.

On 22 August 1984 he was taken to the cardiac catheterisation laboratory where initial subselective injection into the vein graft to the right coronary artery once again showed a long segmental stenosis on the most proximal portion of this vein graft with 80–90% luminal reduction. (Fig 1b). The appearance after the second injection suggested a dynamic component to the stenosis, so we gave additional sublingual glyceryl trinitrate and nifedipine.

Subsequent injection into this vein graft, in right and left anterior oblique views, showed a widely patent proximal vein graft with no evidence of any important stenosis (fig 2).

We concluded that the stenosis was caused solely by venospasm, and angioplasty was not attempted on this vein graft. We then proceeded with the introduction of the balloon dilatation catheter into the native right coronary artery and this catheter was negotiated

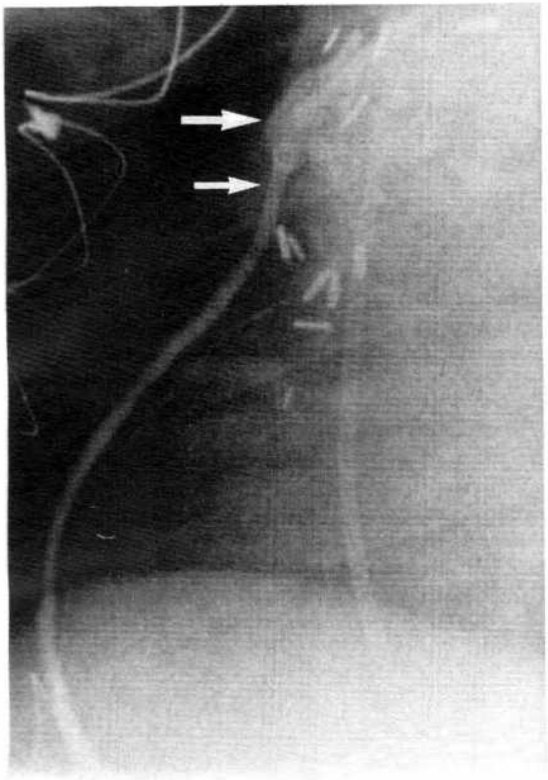

Fig 2 *Vein bypass graft to right coronary artery in left and right anterior oblique projections after administration of sublingual nifedipine and glyceryl trinitrate, showing a return to normal at the site of spasm of the vein bypass graft (small arrow) after subselective dye injections (large arrow).*

across the stenotic segment of the mid portion of the native right coronary artery over a steerable guide wire system. Simultaneous pressure recordings were obtained distal and proximal to the stenotic region; they did not show any gradient.

Because we did not regard the stenosis of the mid right coronary artery as haemodynamically important, angioplasty was not performed. At discharge the patient was taking 80 mg of nifedipine and 40 mg of isosorbide dinitrate in divided doses. The patient remained symptom free during a clinical follow up of 16 months.

Discussion

Long term follow up reports on patients who have undergone coronary artery bypass operation with saphenous vein grafts showed early and late recurrences of symptoms in many.[5-7] These ischaemic symptoms might be caused by disease progression in the grafted and non-grafted vessels, incomplete revascularisation, graft occlusion, atherosclerotic stenosis of a vein bypass graft, technical problem at the heel or toe of the vein graft anastomosis, kinking of the vein graft, and spasm of the saphenous vein bypass graft.[5-11]

In two earlier cases spasm of the saphenous bypass graft occurred in freshly resected or relatively new and young saphenous veins that contained viable and reactive smooth muscle cells within the media.[3 4] We found spasm in an older vein graft that was not expected to contain reactive smooth muscle cells and apparently was a rigid non-reactive conduit.[12-14] This case underlines the fact that the degree and timing of changes in the media of the vein graft can vary and that such variation could allow severe, symptomatic venospasm and recurrence of disabling angina or myocardial infarctions to develop as a result of graft closure. Within a month of operation, vein grafts show inflammatory cell infiltration and variable necrosis of smooth muscle cells in the media. After six months, these grafts show a considerable decrease in the number of smooth muscle cells in the media, which are replaced with fibrous tissue and collagen. Thus the saphenous vein bypass graft becomes stiffer and more fibrous. The degree of these changes varies from one patient to another, from one graft to another in the same patient, and from one segment to another in the same graft.[12-14] After six months, the contractility of these grafts is much reduced.[15 16] So severe spasm of vein graft after the first six months seems unlikely. But our case indicates that severe symptomatic spasm might occur even in older vein bypass grafts despite these histological changes.

Any attempt to explain and understand this unique phenomenon can only be based on the mechanisms suggested for spasm in native coronary arteries. Melville *et al* suggested that coronary spasm is caused by neural impulses from the central nervous system or autonomic nervous system.[17] This hypothesis, however, has been challenged by the results of autotransplantation reported by Clark *et al*.[18] They described severe refactory coronary arterial spasm in a patient with a cardiac transplant. Although this patient became symptom free after transplantation, right coronary artery spasm was provoked by infusion of ergometrine.

It seems, therefore, that coronary spasm can occur in a totally denervated heart. In vivo and in vitro studies showed that vascular tone is balanced by two potent hormones released from platelets and endothelial cells. Thromboxane A_2, released by the platelets, is a powerful vasoconstrictor that has been implicated in coronary artery spasm and genesis of atherosclerosis and early postoperative occlusion of vein bypass grafts. Prostacyclin, a powerful vasodilatating prostaglandin released from endothelial cells, counters the effect of thromboxane A_2 to maintain a balanced vascular tone. When the concentration of thromboxane A_2 is higher than that of prostacyclin, vasoconstriction may occur.[19,20] Platelet aggregation could result in further increase in thromboxane A_2 which in turn may precipitate further spasm, diminished flow, and further aggregation leading ultimately to thrombosis and early postoperative occlusion of vein bypass grafts.

In this case report, there was evidence of some progression of disease in the native right coronary artery. This, however, was not regarded as haemodynamically important in reducing resting coronary flow because there was no pressure drop across the stenosis. Nevertheless, such stenosis may affect maximal flow to such an extent that coronary flow reserve is reduced and symptoms develop on effort.

This patient's symptoms, however, were often unrelated to effort, and in view of the clear demonstration of the spasm of vein graft in two successive studies and the success of treatment with calcium blocking agents and nitrates on the patient's symptoms, we believe that the spontaneous spasm of the vein bypass graft was probably responsible for the patient's symptoms by reducing blood flow to a large distal right branch of the right coronary artery, which was totally occluded proximally to the site of an end-to-side anastomosis of a vein bypass graft.

Stress testing was also subjectively positive; however, his symptoms of shoulder and neck pain with radiation to the left arm during the stress testing were identical to his usual presenting symptoms. We therefore believed that his stress testing, although electrocardiographically silent, represented myocardial ischaemia.

Mechanical vasospasm related to diagnostic catheterisation also seems unlikely because the initial vein graft injections were performed subselectively.

The findings in this case may be an example of a feature that is more common than is generally realised. It may help to explain intraoperative or immediate postoperative deterioration in some patients who have undergone coronary artery bypass operation. It may also be one of the mechanisms responsible for postoperative closure of the vein bypass graft.

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Findings at necropsy in the heart of a patient with anticardiolipin syndrome

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SUMMARY A 40 year old man with a history of myocardial infarction and hypertension presented with transient cerebral ischaemic attacks, aortic regurgitation, a raised erythrocyte sedimentation rate, and thrombocytopenia. The anticardiolipin syndrome was diagnosed and he was treated with prednisolone and warfarin. He died two years later after the development of acute heart failure. At necropsy his heart showed widespread arteriolar thrombosis without vasculitis, recanalised large vessel occlusion, and a "post-inflammatory" valvulitis of the aortic valve.

The term anticardiolipin syndrome is a recent introduction but the disease itself is by no means new. False positive results on serological testing for syphilis were reported in a few patients with systemic lupus erythematosus long before lupus erythematosus cells and other immunological features were detected.[1] These patients and those with the "lupus anticoagulant" were only recently recognised as forming a clinically distinct group that was liable to thrombosis, thrombocytopenia, and recurrent abortion. Although they are often negative for antinuclear factor,[2] they have high titres of antibodies to phospholipids, which for convenience are measured as cardiolipin antibodies. These phospholipid antibodies may play a part in the thrombotic complications[3] but they also interfere with in vitro coagulation tests, hence the confusing term "lupus anticoagulant". Systemic lupus erythematosus and the anticardiolipin syndrome are now regarded as separate but overlapping parts of the autoimmune spectrum.

Recent reports indicate that phospholipid antibodies are common both in young survivors of myocardial infarction[4] and after coronary artery bypass grafting[5]: furthermore, their presence is associated with recurrent thrombotic episodes. Cardiolipin antibodies and the clinical syndrome will be recognised with increasing frequency by cardiologists. In this report we highlight two further cardiac manifestations of the syndrome—aortic valve disease and left ventricular failure caused by small vessel thrombosis.

Case report

A 33 year old man first presented in 1978 with an anterior myocardial infarct. Hypertension and impaired renal function (urea 9·6 mmol/l, creatinine 0·16 mmol/l) were diagnosed five years later. He had an erythrocyte sedimentation rate of 15 mm/h, proteinuria of 0·3 g/day, and a normal intravenous urogram. He was treated with metoprolol and bendrofluazide.

When he was 40 temporal lobe epilepsy developed and a computed tomographic brain scan showed a right parietal infarct. Two months later he was admitted after two transient cerebral ischaemic attacks affecting the right arm. Livedo reticularis was present on his trunk, arms, and legs and aortic regurgitation was noted for the first time. The blood pressure was 140/70 mm Hg and no other abnormal signs were present. He had a normochromic, normocytic anaemia of 102 g/l, a normal white count, and moderate thrombocytopenia (118 × 10^9/l). The erythrocyte sedimentation rate was 100 mm/h.

Infective endocarditis was suspected but blood cultures were sterile. Further investigations showed a normal C reactive protein, C3, and C4 but very high concentrations of C3 degradation products (C3d). Neither antinuclear factor nor DNA antibodies were detected. The activated partial thromboplastin time was prolonged at 59 seconds (normal upper limit 48 s) because a "lupus anticoagulant" was present. Serological testing for syphilis was negative. Cardiolipin antibodies of both IgM and IgG classes were measured by a solid phase enzyme linked immunosorbent assay (ELISA).[6] The result was >6 SD above control samples, and after standardisation of the assay[7] the IgG antibody concentration ranged from 150 to 250 units (normal upper limit 6 units).

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Cross sectional echocardiography showed thickening of the non-coronary cusp of the aortic valve. A biopsy specimen of skin and muscle taken from an area of livedo reticularis showed evidence of venous thrombosis in the subcutis but immunofluorescence was non-specific. A renal biopsy specimen showed only ischaemic changes without evidence of vasculitis or glomerulonephritis.

He was treated with warfarin and prednisolone (30 mg/day) and his haemoglobin and erythrocyte sedimentation rate returned to normal although concentrations of cardiolipin antibody and C3d remained high. Over the next two years he remained well with no change in the clinical signs or cardiothoracic ratio on chest *x* ray, despite a reduction in the dose of prednisolone to 7·5 mg/day. He died suddenly at home after a week of increasing breathlessness and fatigue.

At necropsy the heart was enlarged (580 g). The tricuspid, pulmonary, and mitral valves were normal. The aortic valve (fig 1) had thickened and fibrotic cusps with commissural fusion between the left and non-coronary cusps. There was a small fibrous nodule in the middle of the free margin of the non-coronary cusp, with cusp retraction resulting in functional aortic incompetence. The left ventricle was dilated and hypertrophied (280 g). There was an area of fibrosis in the anterior wall consistent with a previous infarct. Coronary angiography after death showed extensive recanalisation of the left anterior descending artery and a low grade stenosis on the posterior right coronary artery.

Histologically the aortic cusps were thickened and fibrosed. The nodule on the non-coronary cusp was composed of dense fibrous tissue with organising platelet thrombus at the free margin. The features were those of a non-specific "post-inflammatory" valvulitis. The left anterior descending artery showed extensive recanalisation at the site of a small underlying fibrous plaque. Stenosis of the right coronary artery was caused by a small fibrous plaque with overlying platelet thrombus: there was no evidence of plaque fissuring in any of the levels examined.

The most striking finding was the presence of multiple platelet thombi within small intramyocardial arterioles (fig 2); these were present within the territories of all three coronary arteries. Some were

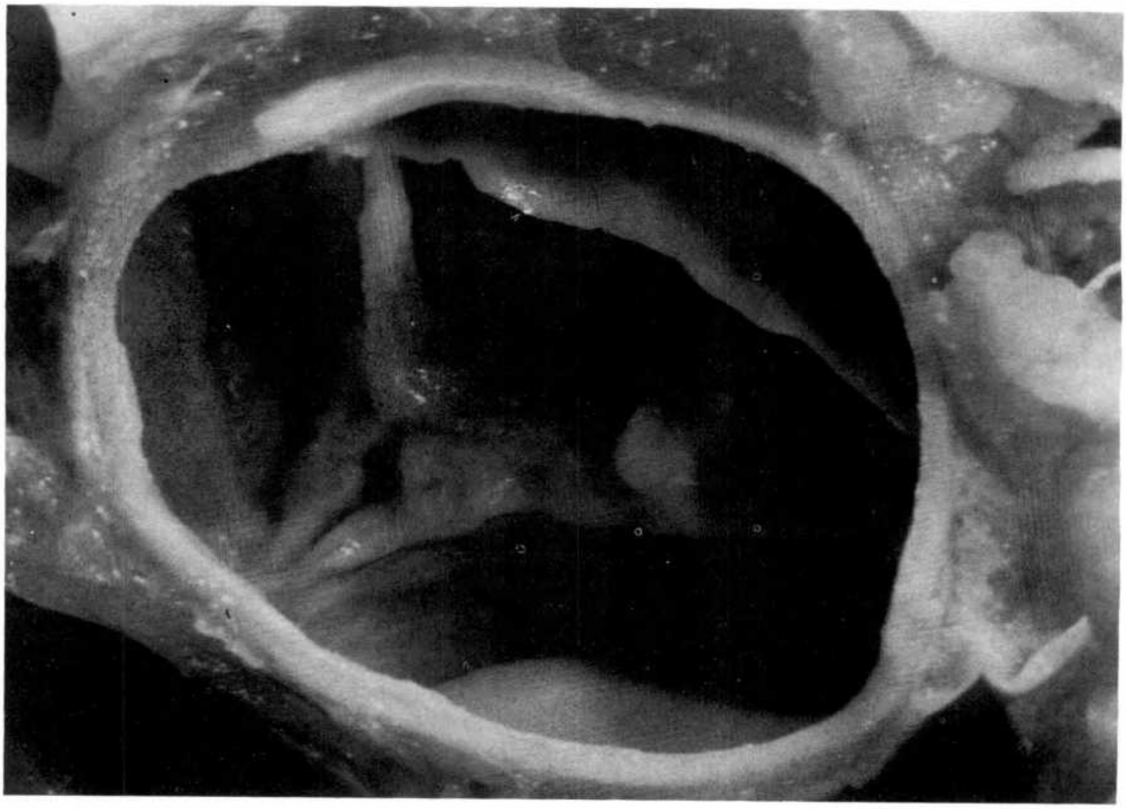

Fig 1 *Aortic valve, viewed from the ascending aorta, showing cusp fusion and nodule formation.*

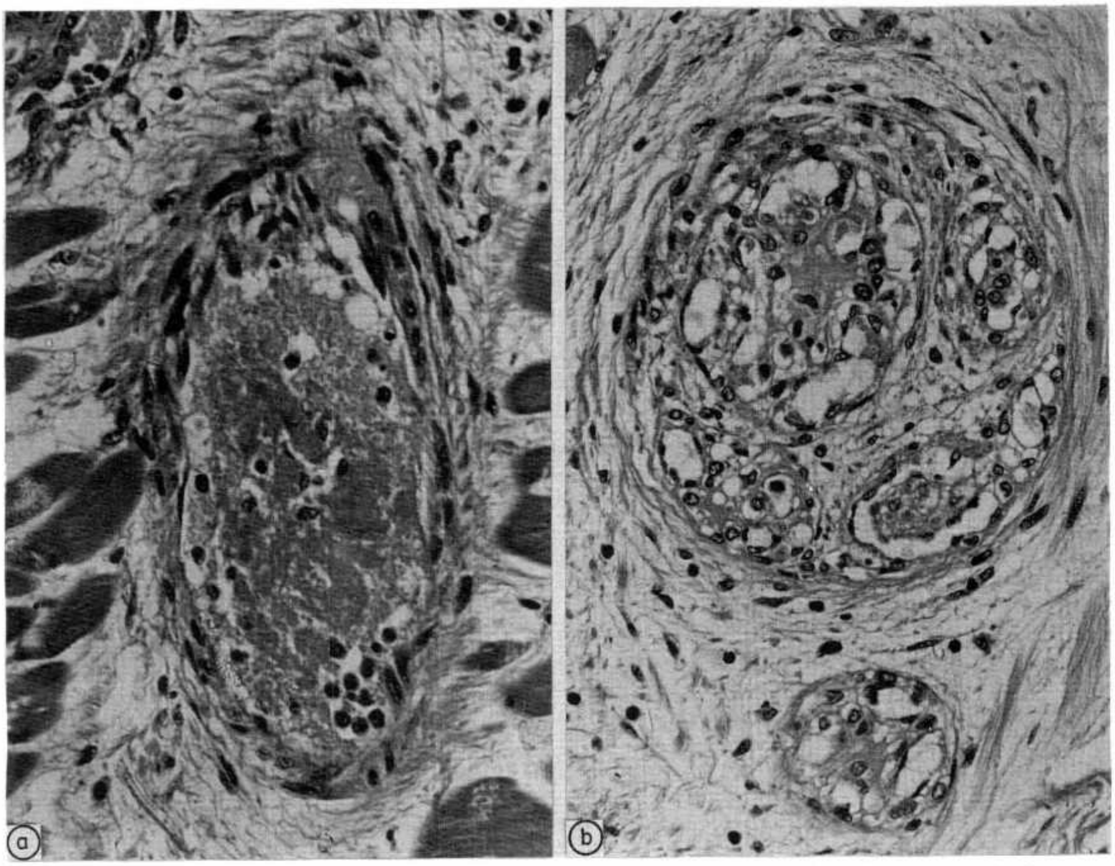

Fig 2 *Two intramyocardial arterioles showing fresh platelet thrombus (a) and extensive recanalisation of organised thrombus (b). Haematoxylin and eosin (original magnification × 370).*

recent while others showed evidence of organisation and recanalisation. Associated with these vascular occlusions were multiple microinfarcts, some of which were recent while others were organised fibrous scars. There were multiple microinfarcts with extensive small vessel occlusion and recanalisation in the brain and kidneys.

There was only slight atheroma of the aorta but there were several intimal plaques measuring up to 5 cm in diameter in the ascending aorta and arch. Histologically these showed fibrous intimal thickening with overlying platelet thrombus, which in places was being incorporated into the intima. Both lungs showed severe pulmonary oedema and there were bilateral adrenal haemorrhages that were thought to be an agonal event, possibly related to anticoagulation. Death was attributed to cardiac failure secondary to diffuse ischaemic myocardial damage.

Discussion

This patient had a history of myocardial and cerebral infarction, hypertension, epilepsy, and renal impairment. He presented with transient ischaemic attacks, aortic regurgitation, and haematological markers of a systemic illness. The clinical and laboratory findings did not support a diagnosis of systemic lupus erythematosus, whereas the features were characteristic of the anticardiolipin syndrome.[1]

The syndrome is characterised by thrombosis, thrombocytopenia, and recurrent abortion; but livedo reticularis, epilepsy, and both systemic and pulmonary hypertension are associated features. Renal disease when present is usually vascular in origin.

Two previous case reports in the *British Heart Journal* have described the thrombotic complications of phospholipid antibodies in patients with systemic lupus erythematosus.[8 9] But while systemic lupus erythematosus and the anticardiolipin syndrome are closely related conditions, which may coexist in the same patient, each may also occur in isolation and the differing clinical and immunological features justify their distinction.[2] This is illustrated by the current case where neither antinuclear factor nor DNA antibodies were detected.

An association between the anticardiolipin syndrome and both aortic and mitral regurgitation is now recognised.[10] The heart is often affected in classic systemic lupus erythematosus[11] but a recent echocardiographic series suggests that endocarditis, valve thickening, and unexplained impairment of left ventricular function occur almost exclusively in those who also have cardiolipin antibodies.[12] In the present case, aortic valve histology showed features of a post-inflammatory valulitis; these changes are non-specific and their association with cardiolipin antibodies remains speculative.

The most important finding at necropsy was widespread microvascular thrombosis affecting myocardial, cerebral, and renal arterioles and resulting in diffuse ischaemic damage. We are not aware of any previous reports of such extensive thrombus of small vessels in the absence of clinical or immunological features of systemic lupus erythematosus. This case extends the range of cardiac lesions associated with cardiolipin antibodies and highlights the typical clinical features of the syndrome.

We thank Professor J R Hampton for permission to report this case and for advice with the preparation of the paper.

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Growth of the pulmonary artery after neonatal balloon dilatation of the right ventricular outflow tract in an infant with the tetralogy of Fallot and atrioventricular septal defect

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SUMMARY A two week old girl with tetralogy of Fallot and atrioventricular septal defect underwent palliation, for severe hypoxaemia, by balloon dilatation to the right ventricular outflow tract. This procedure was repeated once over the next eight months without complications. Serial right ventricular angiograms showed growth of the hypoplastic pulmonary ring ("annulus"), trunk, and arteries.

Balloon dilatation is an alternative palliative procedure for patients with the tetralogy of Fallot which may promote growth of the pulmonary ring, trunk, and arteries.

Surgical systemic to pulmonary artery shunts for tetralogy of Fallot have been shown to produce growth of pulmonary ring, trunk, and arteries.[1-3] Shunt surgery, however, is not without risk and complications such as shunt occlusion, kinking of the pulmonary arteries, and pulmonary hypertension[4-6] can occur. The operative mortality varies from 0% to 13%.[4 7] A recent preliminary study has shown encouraging results of balloon dilatation of the right ventricular outflow tract as an alternative palliative procedure[8]; however, objective evidence of pulmonary artery growth was not evaluated.

We report a case of tetralogy of Fallot with atrioventricular septal defect in which growth of associated hypoplastic pulmonary ring, trunk, and arteries was shown after balloon dilatation of the right ventricular outflow tract.

Case report

A day old girl, birth weight 2·4 kg, presented with severe central cyanosis. Physical examination showed features of trisomy 21 syndrome and an ejection systolic murmur along the left sternal border. A chest *x* ray showed an enlarged heart with oligaemic lung fields. The electrocardiogram showed sinus rhythm with a superior QRS axis. Echocardiography showed an atrioventricular septal defect and tetralogy of Fallot with severe hypoplasia of the pulmonary ring, trunk, and arteries. Treatment with intravenous prostaglandin E_2 was started. Because she was still dependent upon the prostaglandin E_2 after two weeks, palliation with balloon dilatation of the right ventricular outflow tract was performed.

Cardiac catheterisation was performed under general anaesthesia with 100% oxygen. Right ventricular angiograms in anteroposterior and lateral projections (fig 1a and b) showed severe narrowing of the infundibulum and hypoplasia of the pulmonary ring and trunk and small pulmonary arteries (table 1). The diameter of the pulmonary ring was 4·2 mm and several dilatations were initially performed with a Schneider 6 mm diameter balloon catheter. This procedure was then repeated with a Schneider 8 mm diameter balloon catheter. There were no complications during or after the procedure. Oxygen saturation in the femoral artery increased from 84% at the start of the procedure to 92% at the end. Prostaglandin E_2 was then stopped.

Nine weeks later she was readmitted because of hypercyanotic episodes. She was being treated with propranolol (3 mg/kg/24 hours). She had gained weight to 3·86 kg. Haemoglobin was 177 g/l and the haematocrit was 0·536. Balloon dilatation was repeated. Right ventricular angiograms in both the anteroposterior and lateral projections showed that there had been an increase in size of the pulmonary ring (which now measured 6 mm), the pulmonary

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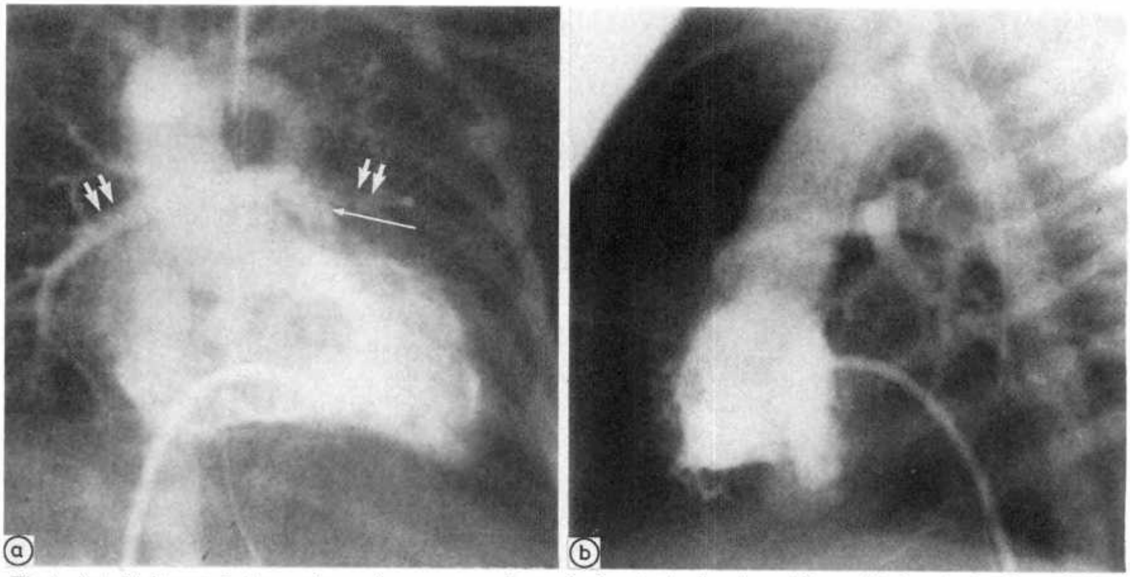

Fig 1 *(a) Right ventricular angiogram in anteroposterior projection obtained at time of first palliation showing hypoplasia of the pulmonary ring, trunk (single arrow), and arteries (double arrows). (b) Lateral projection of the same right ventricular angiogram.*

Table 1 *Angiographic measurements corrected for magnification*

	Dimensions (mm)						
Catheter	*PR*	*PT*	*RPA (D)*	*RPA (P)*	*LPA (D)*	*LPA (P)*	*DsAo*
1	4·2	4·2	3·2	3·2	3·7	3·7	6·1
2	6·0	4·0	5·6	4·8	4·0	3·7	6·0
3	6·7	6·4	8·9	8·1	5·8	6·2	6·9

PR, pulmonary ring; PT, pulmonary trunk; RPA, right pulmonary artery; LPA, left pulmonary artery; (D), distal; (P), proximal; DsAo, descending aorta.

trunk, and arteries (table 1). Several inflations were performed with 8 mm and 9 mm Schneider balloon catheters. Femoral arterial saturation increased from 56% to 73% while she was treated with 50% oxygen. Propranolol was then withdrawn.

Five months later she was readmitted with moderate central cyanosis. The haemoglobin was now 196 g/l with a haematocrit of 0·644. She had continued to grow and now weighed 5 kg. Repeat cardiac catheterisation and angiocardiography of the right ventricle showed further growth of the pulmonary ring, trunk, and arteries (table 1). In addition, there was moderate supravalvar stenosis and the infundibulum also seemed less narrow (fig 2). She subsequently underwent a successful right modified Blalock-Taussig shunt procedure.

ANGIOGRAPHIC MEASUREMENTS

Most measurements were recorded from right ventricular angiograms in the anteroposterior projection, although in a few cases the lateral projection was used. Measurements were taken to the nearest 0·5 mm and then corrected for magnification. The

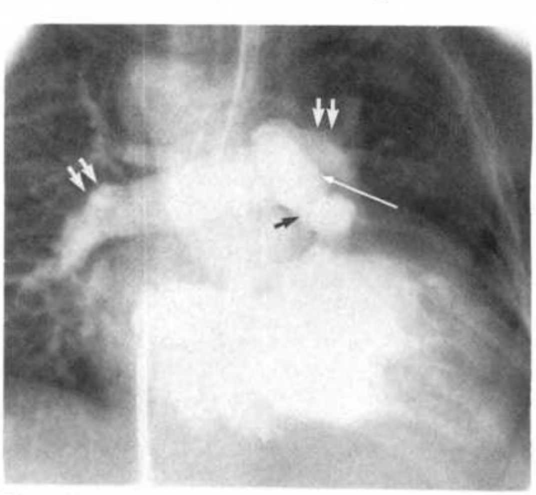

Fig 2 *Right ventricular angiogram in anteroposterior projection obtained at third cardiac catheterisation. The pulmonary ring trunk (single white arrow) and arteries (double arrows) had increased in size. There was also evidence of supravalvar pulmonary stenosis (black arrow).*

Table 2 *Angiographic measurements normalised by use of the ratio to the descending aorta*

Catheter	*PR*	*PT*	*RPA*	*LPA*
1	0·69	0·69	0·52	0·6
2	1·0	0·67	0·93	0·67
3	0·97	0·92	1·29	0·84

PR, pulmonary ring; PT, pulmonary trunk; RPA, right pulmonary artery; LPA, left pulmonary artery; DsAo, descending aorta.

pulmonary ring and trunk were measured during early systole and again in mid-diastole and the average value was taken. The pulmonary artery was measured just distal to the bifurcation and just proximal to the origin of the first branch at end systole. The descending thoracic aorta was measured at the level of the diaphragm, also at end systole.

The dimensions of the pulmonary ring, trunk, and artery were then normalised by using their ratio with the descending thoracic aorta[9] (table 2). We calculated predictive postoperative right ventricular/left ventricular pressure ratios by the methods described by Blackstone and colleagues.[10] Measurements taken from the first angiogram gave a predictive ratio of 0·63 for correction by a conduit or transannular patch and 0·82 for straightforward correction. The predictive ratios calculated from the final angiogram were 0·43 and 0·59 respectively.

Discussion

The mortality for primary correction of tetralogy of Fallot is between 1% and 5%.[11] Young age and small pulmonary arteries are important risk factors and many centres would perform an initial palliative procedure to encourage growth of the pulmonary arteries.[12] Palliative operations including closed pulmonary valvotomy and infundibular resection (Brock's procedure) and systemic to pulmonary artery shunts have all been shown to promote growth of the pulmonary valve annulus and pulmonary arteries.[1 3 13] The subsequent need for a transannular patch is reduced and operative risks are decreased. These operations are, however, associated with serious complications and a considerable mortality.

Complications after closed pulmonary valvotomy and infundibular resection include heart failure and inadequate relief of symptoms requiring a second palliative procedure. The mortality is around 15%.[13] Blalock-Taussig shunts are associated with early and late occlusion in approximately 10%,[4] with a significantly higher rate of late occlusion occurring in children less than four weeks of age at the time of shunt insertion.[7] The operative mortality varies between 0% and 8%.[7 4 14] Waterston shunts are associated with complications[5 6] of pulmonary vascular disease and serious kinking, usually of the right pulmonary artery, in up to 16%. The operative mortality is between 5% and 13%.[7 15] Since mortality for total correction of tetralogy of Fallot and atrioventricular septal defect is high (27% hospital mortality[11]) the operation is usually delayed until the patient is older and this delay is dependent on successful long term palliation. In view of these problems balloon dilatation of the right ventricular outflow tract has been suggested as an alternative palliative procedure.[8]

In our patient balloon dilatation was an attractive palliative procedure because it could potentially delay the shunt operation until the patient was older and consequently increase the chance of the shunt remaining patent for longer. Dilatation gave adequate palliation for eight months but more importantly it resulted in the additional benefit of pulmonary artery growth with its associated advantages.

To examine pulmonary artery growth we used normalised measurements (growth of the descending aorta was assumed to be constant) by a method already used in infants and children.[1 2 9] We found that over the study period the pulmonary ring, trunk, and arteries grew more rapidly than normal. Another method of indirectly assessing pulmonary artery growth is by using the calculations described by Blackstone to predict postoperative right ventricular/left ventricular pressure ratios.[10] A predicted ratio around 0·85 after correction without the use of a transannular patch or conduit is generally felt to be unacceptably high and indicates that a transannular patch or at least a conduit will be necessary. A ratio of 0·82, obtained in our patient at the time of the first catheter, suggests a transannular patch would probably have been required if early corrective operation had been contemplated. At the time of the final catheter, however, this ratio had fallen to 0·59, suggesting that a transannular patch is now less likely to be required at correction and this indirectly implies pulmonary artery enlargement.

In a report of a series of 24 balloon dilatations in infants with tetralogy of Fallot 21 were uncomplicated.[8] The results were encouraging, with 73% of the patients successfully palliated for a mean period of 8·5 months. However, in this series the growth of the pulmonary arteries after balloon dilatation was not commented on. We believe that balloon dilatation of the right ventricular outflow tract is a safe, effective palliative procedure for the tetralogy of Fallot that may additionally promote growth of the pulmonary ring, trunk, and arteries.

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Successful repair of an atrial septal defect associated with right to left shunting

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SUMMARY An atrial septal defect was successfully repaired in a young woman despite the presence of pulmonary hypertension and right to left shunting. Before repair both isoprenaline infusion and 100% inspired oxygen produced significant falls in pulmonary artery pressure and pulmonary vascular resistance. A lung biopsy specimen at operation indicated a considerable decrease in the concentration of parenchymal pulmonary arteries and an absence of intimal fibrosis or medial hypertrophy.

Pulmonary artery banding performed in infancy, as part of the management of a ventricular septal defect, may have contributed to the underdevelopment of the pulmonary vascular tree. The reduced number of pulmonary arteries is a possible explanation for the pulmonary hypertension.

It is uncommon for an isolated atrial septal defect to be associated with right to left shunting unless severe pulmonary hypertension is present. Operation is usually not recommended in such patients. We report a young patient with an atrial septal defect associated with pulmonary hypertension and right to left shunting who underwent successful repair. We believe that underdevelopment of the pulmonary tree, which was shown by lung biopsy, was associated with a pre-existing ventricular septal defect and pulmonary artery banding.

Case report

As an infant the patient presented with heart failure and a murmur was detected. She was acyanotic and at catheterisation at the age of nine months the atrial septum was crossed and a left to right shunt at the ventricular level was shown. Pulmonary artery pressure was not measured. Right and left ventricular systolic pressures were 51 mm Hg and 80 mm Hg respectively. Medical management was recommended and catheterisation (at age two) confirmed a left to right shunt at the ventricular level and pulmonary hypertension (table 1). Infusion of tolazoline hydrochloride resulted in a small fall in pulmonary resistance and an increase in the pulmonary systemic flow ratio. Pulmonary artery banding was performed.

When she was three and a half years old repeat catheterisation indicated a bi-directional shunt at the ventricular level. There was a 20–36 mm Hg peak systolic gradient across the region of the band and the distal pulmonary artery pressure was raised (64/30 mm Hg). The ventricular septal defect was closed and the band removed; apart from several early postoperative episodes of cyanosis the subsequent course was uneventful.

At the age of 19, when she was 20 weeks pregnant, the patient presented with haemoptysis, and an initial diagnosis of pulmonary embolism was excluded by pulmonary angiography. A limited study of the right heart showed pulmonary artery pressure of 55/22 (mean 35 mm Hg). Bi-directional shunting at the atrial level with a small net right to left shunt was detected. Table 1 does not include the results of this study. The arterial oxygen saturation was 88% on room air. Subsequent bronchoscopy showed prominent submucosal vessels in the bronchi and it was thought that rupture of these vessels had caused the haemoptysis. Physical findings included an active right ventricle on palpation, wide fixed splitting of the second heart sound, and a soft ejection systolic murmur along the upper left sternal border. There was no evidence of clubbing. The electrocardiogram showed sinus rhythm, right axis deviation, and right ventricular hypertrophy. Chest *x* ray showed a normal sized heart and normal vascular pattern. A cross

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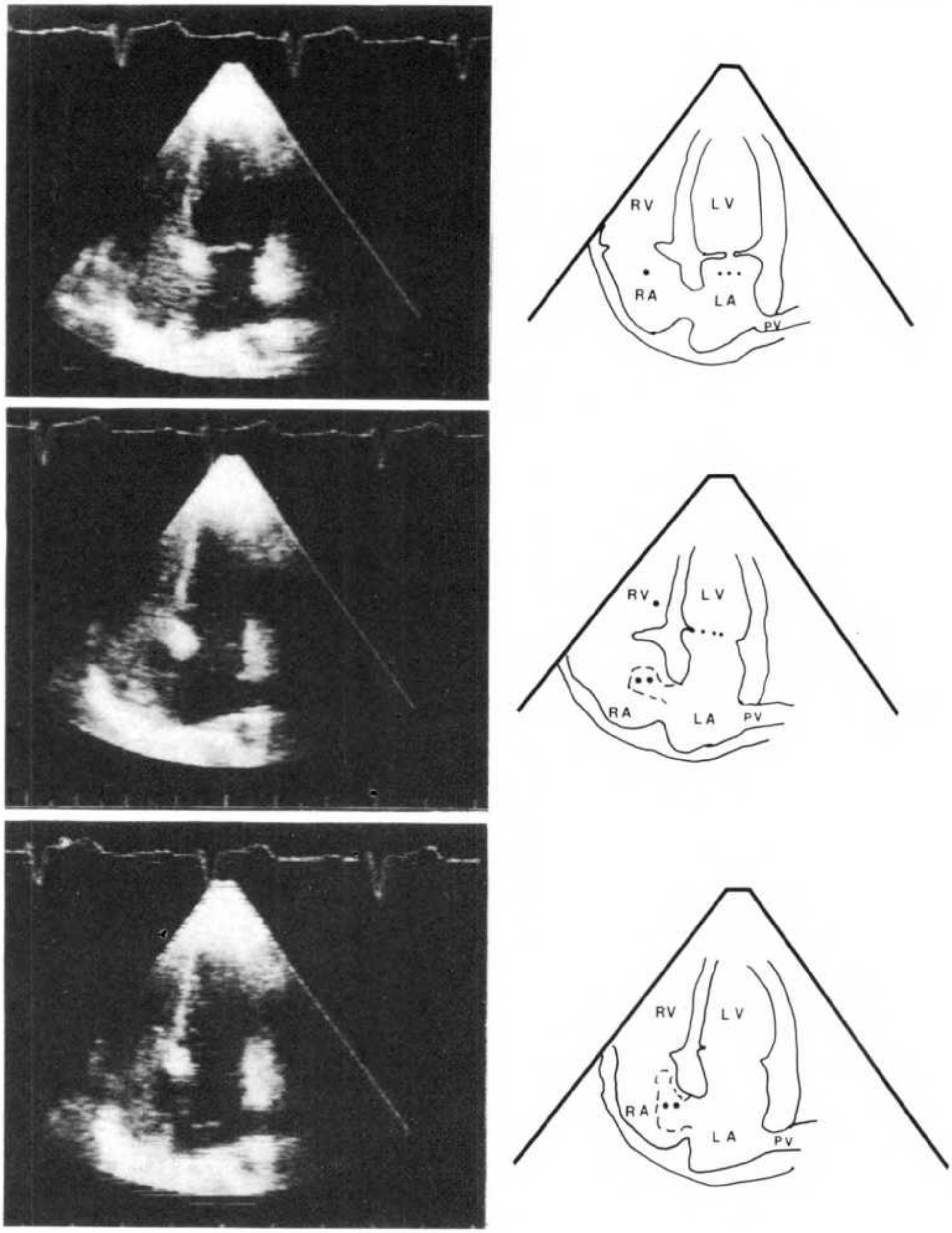

Fig 1 *Sequence of cross sectional images recorded from the apical four chamber acoustic window and corresponding line drawings of a saline injection showing a bi-directional shunt at atrial level. Top panel: this systolic frame shows deviation of the interatrial septum toward the left atrium and microbubbles (*) filling the right atrium and also the left atrium (***). Middle panel: this shows a diastolic frame with microbubbles in the orifice of the mitral valve (***) and entering the left ventricle. A small area of washout is seen in the right atrium (**). Bottom panel: this is the next frame in the cycle and the negative area in the right atrium is larger (**). LA, left atrium; LV, left ventricle; PV, pulmonary vein; RA, right atrium; RV, right ventricle.*

Table 1 *Results of cardiac catheterisation*

	Age								
Age	*9·5 month*	*2 yr*		*3·5 yr*		*19·5 yr*		*20 yr*†	
Intervention	—	—	T	—	—	I	100% O_2	—	I
Right atrium (mean mm Hg)	—	—	—	—	4	2	3	4	3
Right ventricle (mean mm Hg)	51/0	82/0	—	100/ 0	60/ 3	—	—	55/ 4	—
Main pulmonary artery									
systolic/diastolic	—	84/32	85/30	64/30	55/30	45/32	42/24	55/25	70/30
(mean mm Hg)	—	42	47	43	43	38	30	38	45
Left atrium (mean mm Hg)	8	8	—	—	5	3	3	6	3
Left ventricle (mm Hg)	80/ 0	100/ 6	—	—	130/ 5	—	—	—	—
Aorta									
Systolic/diastolic	—	100/50	100/60	115/52	130/70	105/55	125/70	122/68	145/55
Mean pressure (mm Hg)	—	63	66	72	82	82	90	82	78
Pulmonary resistance (units/m²)	—	5·6	3·9	9·5	13·8	7·5	8·1	9·5	6·4
Systemic resistance (units/m²)	—	19	21	21	21	14	28	20	11
Cardiac index (l/min/m²)	3·1*	3·3*	3·2*	3·5*	3·9	6·0	3·2	4·0	7·0
Pulmonary flow/systemic flow	1·7/1	2·3/1	3·8/1	1·3/1 +	0·8/1 +	0·84/1 +	1·2/1 +	1	1
Left to right shunt (l/min/m²)	2·2	4·2	8·8	1·6	0·27	0·54	0·8	0	0
Right to left shunt (l/min/m²)	0	0	0	0·6	1·07	1·51	0·3	0	0

*Assuming an oxygen consumption of 120 ml/min/m². †Six months after closure of the atrial septal defect. I, isoprenaline; T, tolazoline hydrochloride; + , bi-directional shunt.

sectional echocardiographic study with saline injection showed bi-directional shunting at the atrial level (fig 1). Because of hypoxia the patient was prescribed supplemental nasal oxygen which eliminated the arterial desaturation. The patient tolerated vaginal delivery at 34 weeks' gestation. The premature infant was well at discharge.

After delivery, repeat catheterisation (table 1) showed moderate pulmonary hypertension, and isoprenaline infusion reduced the pulmonary vascular resistance from 13·8 units/m² to 7·5 units/m². The arterial oxygen saturation on room air was 83%. There was a bi-directional shunt at the atrial level with a net right to left shunt. The pulmonary systemic flow ratio increased from 0·8 to 0·84 with isoprenaline infusion. When the patient breathed 100% oxygen pulmonary artery pressure fell and the net shunt was left to right. Contrast injection in the

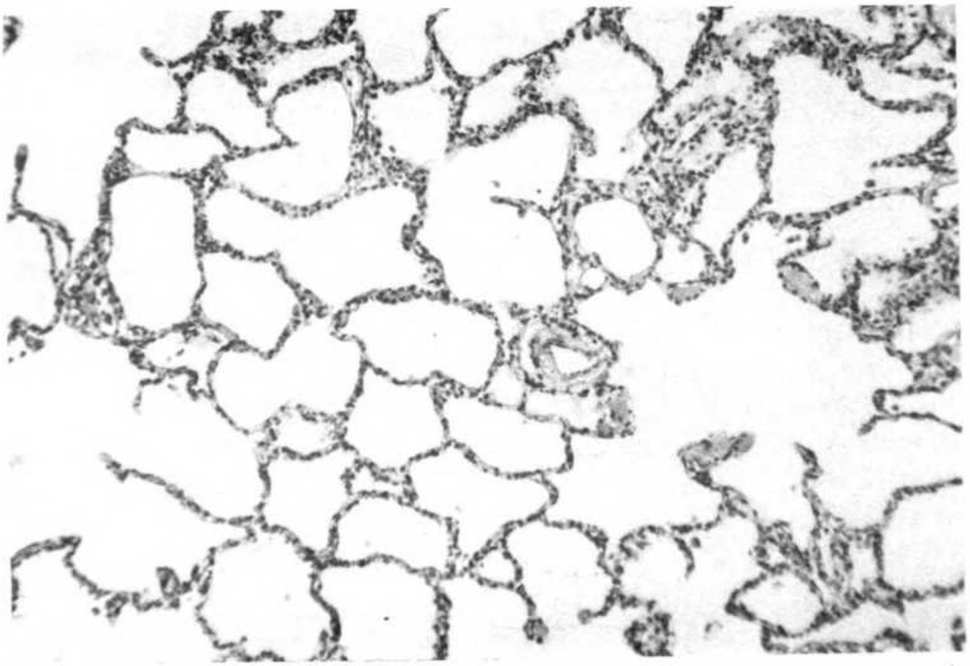

Fig 2 *A section of the lung biopsy specimen showing the paucity of parenchymal arteries. Only one artery is seen centrally.*

inferior vena cava showed flow across the interatrial septum and left to right shunting on recirculation. Left ventricular cineangiography indicated an intact ventricular septum. A 1 × 2 cm atrial septal defect was surgically closed.

A lung biopsy (fig 2) performed at operation showed that the density of the small arteries was reduced; the ratio of pulmonary arteries to alveoli was 1:18 (normal for this age, 1:6). The ratio was assessed by examining a number of fields although only one artery is shown in the figure. Intra-acinar arteries appeared to be dilated but without evidence of muscular hypertrophy. Pre-acinar arteries showed minimal muscular hypertrophy without intimal lesions. The alveolar walls were delicate without fibrosis and the radial alveolar count of 10 was within the normal range.

Catheterisation (table 1) performed six months after operation indicated no evidence of shunting and the pulmonary vascular resistance fell from 13·8 units/m^2 before operation to 9·5 units/m^2 after operation. The results of exercise testing performed six months and 18 months after operation showed improvement in exercise capacity (table 2). Postoperatively there was no significant desaturation with exercise.

Discussion

The initial presentation during pregnancy with signs of pulmonary hypertension and arterial desaturation suggested progressive pulmonary hypertension. Proximal pulmonary artery thrombosis has been reported as a cause of this[1] and was excluded by the normal pulmonary angiogram.

Table 2 *Results of treadmill exercise testing*

	Preoperative	*Postoperative 6 months*	*Postoperative 18 months*
Exercise duration (min) (Bruce protocol)	6·2	7·2	8·1
Heart rate (beats/min):			
Rest	100	82	64
Maximal	163	163	172
Systolic blood pressure (mm Hg):			
Rest	118	110	102
Maximal	142	160	152
Diastolic blood pressure (mm Hg):			
Rest	64	60	68
Maximal	54	60	76
Peak oxygen consumption (ml/kg/min)	12·5	19·1	18·4
Oxygen saturation (%):			
Rest	93	97	—
Maximal	79	94	—

After closure of a ventricular septal defect most infants show resolution of pulmonary hypertension; however, a few became worse. Before the pulmonary artery banding the pulmonary vascular resistance was raised and there was further increase after the band was placed. The postoperative pulmonary resistance at the age of 20 was very similar to that at the age of three and a half.

The pulmonary vascular resistance (13·8 units/m^2) and arterial desaturation are adverse prognostic factors for operation.[2] The reduction in resistance with isoprenaline and when 100% oxygen was breathed suggested considerable pulmonary vascular reactivity. The value of 7·5 units/m^2 was similar to that at which others recommend closure of a ventricular septal defect associated with pulmonary hypertension.[3] However, a lower resistance value can be associated with histological evidence of severe pulmonary vascular disease.[4]

The development of the alveolar region starts prenatally. The number of alveoli increases until about eight years of age and the growth of intra-acinar arteries follows that of the alveoli.[5-7] The period of most rapid growth is before the age of three.[7,8] The density of small arteries increases more than alveolar density such that the ratio of arteries to alveoli at birth is 1:20, but by adulthood it is 1:6.[9] Muscularisation of these distal arteries lags, and the adult pattern of muscularisation as related to size does not develop until late childhood or early adulthood.[5,7,9,10]

Reduction in arterial density (graded by the Reid-Rabinovitch system) is a late finding in pulmonary hypertension caused by congenital heart disease. It is usually associated with muscular hypertrophy of the pre-acinar and intra-acinar arteries and correlates with a moderate to severe increase in pulmonary vascular resistance.[9,11]

Growth of the pulmonary vascular bed may have been affected before banding and a decrease in the number of intra-acinar pulmonary arteries has been reported in infants with large ventricular septal defects.[12] Between the time of banding and repair of the ventricular septal defect (when the patient was three and a half) pulmonary vascular resistance increased from 5·6 units/m^2 to 9·5 units/m^2, pulmonary blood flow decreased, and mean pulmonary artery pressure remained the same. It may be that pulmonary artery banding in this patient at the age of two may have contributed to the hypoplasia of the pulmonary vascular bed by reducing pulmonary blood flow during the period of pulmonary arterial growth. Although the pressure drop across the band was modest it reduced pulmonary flow considerably and caused a net right to left shunt. In animal models banding of the pulmonary artery decreased the density of the parenchymal arteries.[13] A similar decrease in density of the parenchymal arteries has been found in neonates with pulmonary atresia.[14] Occlusion of the alveolar wall arteries was detected in several patients with pulmonary hypertension associated with congenital heart disease, and it was suggested that this helped explain the reduction in intra-acinar arterial numbers.[15] A reduction in distending pressure was suggested as a possible mechanism for this. In the patient we studied the banding reduced systolic pulmonary artery pressure from 85 to 64 mm Hg while pulmonary vascular resistance increased. There are not sufficient abnormalities in the pre-acinar arteries to explain the persistent pulmonary hypertension, and the intra-acinar arteries seem to be morphologically normal without an abnormal degree of muscularisation. This suggests that the persistent pulmonary hypertension is secondary to hypoplasia of the pulmonary vascular bed.

Most patients with an atrial septal defect associated with severe pulmonary hypertension will not benefit from closure. However, a few like this patient, who show a reduction in pulmonary hypertension with pharmacological agents may be candidates for closure. A preoperative lung biopsy may be helpful in deciding on management. Recognition of the histological pattern of reduced parenchymal arteries on lung biopsy may help to explain pulmonary hypertension. The lack of intimal fibrosis or medial hypertrophy in the pulmonary arteries is unusual given the degree of pulmonary hypertension.

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Severe pulmonary hypertension in Ullrich-Noonan syndrome

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SUMMARY A 19 year old woman with Ullrich-Noonan syndrome presented with a six month history of progressive dyspnoea and cyanosis. Clinical features were suggestive of severe pulmonary hypertension. Cross sectional echocardiography showed pronounced right ventricular pressure overload with right ventricular hypertrophy. Cardiac catheterisation confirmed severe pulmonary hypertension. Attempts to reduce pulmonary artery pressure with calcium channel blockers were unsuccessful. The patient died shortly after investigation. Necropsy confirmed primary pulmonary hypertension.

The Ullrich-Noonan syndrome is an autosomal dominant condition of both sexes in which the affected individuals have many of the phenotypic features of Turner's syndrome, but with a normal karyotype and normal secondary sexual characteristics. There is a predisposition to cardiac anomalies, the most commonly described being pulmonary valve stenosis (often associated with an atrial septal defect) and asymmetrical septal hypertrophy.[1-3] We report a case of severe primary pulmonary hypertension occurring in association with this syndrome and describe the clinical features and pathological findings of a plexogenic arteriopathy.

Case report

A 19 year old woman was admitted to hospital with a six month history of progressive dyspnoea on exertion. Ullrich-Noonan syndrome was diagnosed when she was two years old and since infancy her exercise tolerance had been reduced by dyspnoea. In the six months before presentation she could only walk 200 metres. This limitation was associated with central cyanosis and a tight central chest pain which resolved on resting. There was no history of syncope. She was also profoundly deaf, but of normal intelligence. Both parents were also profoundly deaf, and her father had the Ullrich-Noonan syndrome. She also had a 17 year old sister with the same syndrome, but with normal hearing, in whom pulmonary stenosis was diagnosed at four months.

She was short with mild neck webbing, hypertelorism, bilateral ptosis, cubitus valgus, and widely spaced nipples. She had normal secondary sexual characteristics. There was mild central cyanosis but she was not dyspnoeic at rest. She had a small volume regular pulse and blood pressure of 130/70 mm Hg in all limbs. The jugular venous pulse was not elevated. There was a prominent right ventricular heave. There was a loud pulmonary component of a narrowly split second heart sound. Examination of the chest was clear, with no peripheral murmurs.

Haemoglobin was 169 g/l. The chromosomal karyotype was normal. The electrocardiogram showed right axis deviation and right ventricular hypertrophy. The chest radiograph confirmed a normal cardiac diameter with normal lung fields. Cross sectional echocardiography showed hypertrophy of a small right ventricle and bulging of the septum into the left ventricle during systole and diastole consistent with a considerable right ventricular pressure overload (fig 1). There was mild tricuspid incompetence on colour flow Doppler ultrasound. The pulmonary artery and its branches and the pulmonary valve were normal. The right atrium was not enlarged. The left heart chambers and valves were normal. The interatrial and interventricular septa seemed to be intact.

Angiography showed a small interatrial communication but no ventricular septal defect or ductus arteriosus. The left ventriculogram was normal. Tables 1 and 2 show basal haemodynamic data and oxygen saturations. The patient was given 60% oxygen over five minutes with continuous measurement of pulmonary artery and aortic pres-

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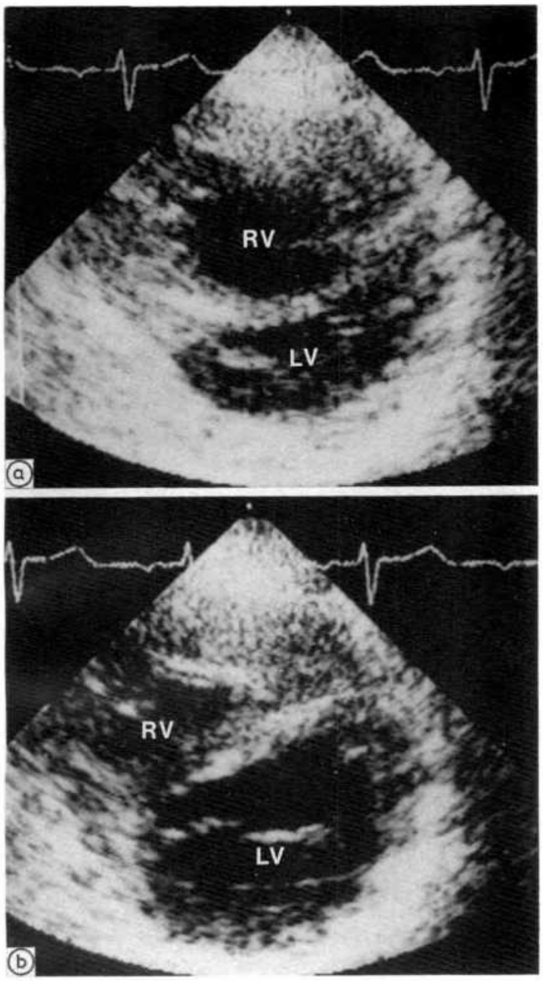

Fig 1 *Cross sectional echocardiogram in the short axis showing (a) compression of the left ventricular cavity by the hypertrophied right ventricle in late systole and (b) flattening of the interventricular septum in late diastole.*

sures (tables 1 and 2). The pulmonary artery catheter was left in place and the patient was given anticoagulants. A trial of hourly oral calcium channel blockers was begun, but nicardipine (three doses of 20 mg), diltiazem (12 doses of 60 mg), and nifedipine (four doses of 20 mg) did not lower the pulmonary artery pressure.

She died suddenly two weeks later. At necropsy, gross right ventricular hypertrophy and anatomical changes of pulmonary hypertension were confirmed. The interatrial septum was thinned, and two slit-like defects were found (1·1 × 0·3 cm and 0·9 × 0·2 cm) in a poorly displayed fossa ovalis. There was no evidence of sepsis, peripheral pulmonary stenosis, or thromboembolic disease. Sections of the lung showed extensive diffuse thickening of the arteriolar walls with medial hypertrophy of the immediate precapillary vessels. Most vessels showed intimal proliferation (fig 2a). There were numerous angiomatoid and plexiform lesions in all areas (fig 2b). Fibrinoid necrosis was seen focally in the plexiform lesions. These features suggested severe pulmonary hypertension of histological grade 4 on the Heath and Edwards classification.[4]

Table 1 *Dynamic pressure and saturation measurements during cardiac catheterisation*

	At rest		*60% O_2 (5 min)*	
Site	*Pressure (mm Hg)*	*Saturation (%)*	*Pressure (mm Hg)*	*Saturation (%)*
Right atrium	$\bar{5}$	68	$\bar{6}$	74
Right ventricle	140/8	68	140/8	—
Main pulmonary artery	$140/50, \overline{80}$	68	$140/50, \overline{80}$	72
Left pulmonary veins		100		100
Left atrium	$\bar{5}$	93	—	—
Left ventricle	120/8	90	110/8	—
Aorta	$120/80, \overline{95}$	88	$110/80, \overline{80}$	98

$\bar{x}$, mean pressure.

Discussion

The commonest cause of pulmonary hypertension in children and young adults is an intracardiac shunt. It has been suggested that pulmonary hypertension occurs in up to 15% of patients with atrial septal defects,[5] but is rare before the third decade.[6 7] Primary pulmonary hypertension is a rare disease that usually occurs in young women (aged 15–40).[8 9]

We believe that the severe pulmonary hypertension described in this patient is likely to be of the

Table 2 *Estimated arterial blood flows and calculated vascular resistances*

Variable	*At rest*	*60% O_2 (5 min)*
Flows:		
Systemic blood flow index (QsI) (l/min/m^2)	3·51	2·70
Pulmonary blood flow index (QpI) (l/min/m^2)	2·19	2·70
Right to left flow (l/min/m^2)	1·32	0
Left to right flow (l/min/m^2)	0	0
QpI:QsI	0·62:1	1·00:1
Resistances:		
Systemic vascular resistance index (RsI) (units.m^2)	25·6	27·4
Total pulmonary resistance index (units.m^2)	36·5	29·6
Pulmonary vascular resistance index (RpI) (units.m^2)	34·2	27·8
RpI:RsI	1·34:1	1·01:1

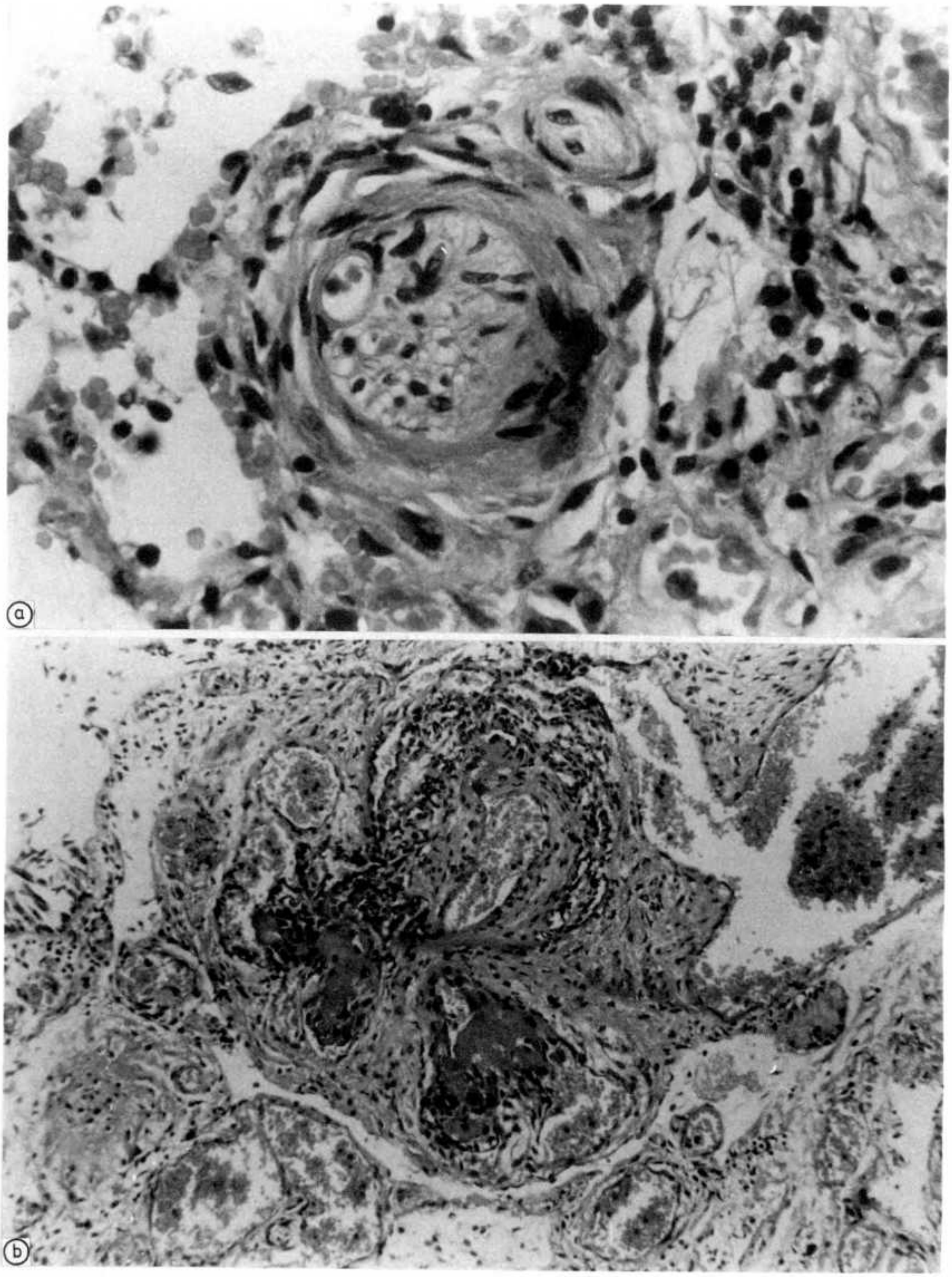

Fig 2 *(a) Pulmonary arteriole showing intimal proliferation and medial thickening (haematoxylin and eosin; original magnification, × 400). (b) Angiomatoid lesion showing fibrinoid necrosis (haematoxylin and eosin; original magnification, × 200).*

primary type. The small atrial septal defects seem to be insignificant in view of hypertrophied, but not dilated, right ventricle and normally sized right atrium, which would exclude a previous large pretricuspid shunt.[10] Pulmonary hypertension secondary to atrial septal defects is associated with cardiomegaly (cardiothoracic ratio $>0{\cdot}6$) in both older,[11] and younger patients.[7] In this case, the cardiothoracic ratio was $<0{\cdot}5$. There has been only one reported case of the Eisenmenger syndrome in association with an atrial septal defect at this age.[6] Other features supporting primary type hypertension are the rapid clinical deterioration and the very high pulmonary artery pressure and pulmonary vascular resistance. In addition, the presence and widespread distribution of dilated plexiform and angiomatoid lesions suggest a primary defect.[12–14]

The treatment of severe pulmonary hypertension is unsatisfactory, in the absence of a remediable cause. Because of the unproven hypothesis that vasoconstriction is important in the pathophysiology of primary pulmonary hypertension, vasodilating agents have been used as treatment, with disappointing results.[15] A recent short term improvement, however, was achieved in pulmonary artery haemodynamic function with regression of right ventricular hypertrophy with calcium channel blockers.[16,17] Though the patient reported here showed partial reversibility of the pulmonary vascular resistance during administration of high flow oxygen (table 2), the calcium channel blockers did not affect pulmonary artery pressure or pulmonary vascular resistance.

The small atrial communication does not seem to be relevant to the pulmonary hypertension. The clinical and pathological features suggest the development of primary pulmonary hypertension in this patient with the Ullrich-Noonan syndrome. This association has not been previously described.

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Br Heart J 1989;62:78–9

Book review

Canadian cardiology

Pioneers of Cardiology in Canada 1820–1970: The Genesis of Canadian Cardiology. Harold N Segall (pp 525: no price given) Willowdale, Ontario: Hounslow Press, 1988. ISBN 0-88882-105-0.

At the age of 91, Harold Segall is not only the doyen of Canadian cardiology but also a link with important figures in British cardiology going back to the years immediately after the first world war when he studied with Starling at University College, London, and indeed, as I understand from other sources, visited Mr S Shaw, the Lancashire jeweller who had made Mackenzie's polygraph. His account is mainly a compendium of various Canadian cardiologists up to 1970 and provides the raw material for a more analytical study that will doubtless appear in due course. Nevertheless, the contributions of important Canadian cardiologists are indicated and some of these deserve special mention.

Segall presents his material in terms of technical advances and many of the sections are preceded by accounts of such developments more generally, sometimes but not always with greater detail than available elsewhere. What emerges from the outset are the different links between French Canadian and English speaking cardiologists and their respective home countries. Pierre Beaubien studied in Paris from 1816 to 1827 and for some time worked at the same hospital as Laennec—though it seems that an unknown student from Newfoundland may have been the first to bring a stethoscope to what is now Canada. Percussion was certainly mentioned in the first Canadian medical journal, *Le Journal de Médecine de Québec*, which was published briefly in the years 1826–27 by Dr X Tessier. A member of the staff of the Montreal General Hospital and one of the four founders in 1823 of the first Canadian medical school based at the hospital, Andrew Fernando Holmes seems later to have used the stethoscope routinely.

William Osler justly gets ample mention. A Montreal graduate, he started his cardiac contributions while at McGill where he almost certainly described the first case of mitral valve prolapse. Maude Abbott became his disciple and was the founder of our modern understanding of congenital heart disease. One of the first modern cardiac pathologists was John George Adami, who emigrated from England in 1892 to become the first professor of pathology at McGill; before he moved there, he had made important studies on pulse recordings at Cambridge. One of the many McGill graduates who found a niche elsewhere was Harry Goldblatt, whose work on renin and on unilateral renal disease as a cause of hypertension is still so fundamental.

Among outsiders who had a potent influence on the development of Canadian cardiology was Sir James Mackenzie, who visited Toronto for the British Medical Association meeting there in 1906, when he gave papers on heart block and hypertensive heart failure. Many of those who heard him and their pupils subsequently came to London to study with him or his successors including John Parkinson, although when electrocardiography was established, Thomas Lewis was the great magnet. While many of the English speaking Canadians included a side visit to Paris, the French Canadians tended to go directly there and came under the influence of Vaquez, Clerc, and Laubry. There seems to have been little mutual communication, and developments in the English speaking and French worlds, which were of a somewhat different nature, were not synthesised in Canada. These differences go right down to the sort of instruments that they obtained. On the whole the anglophones came back with Cambridge recorders while those who went to France brought back electrocardiographs made by the Boulitte company.

Another link with British cardiology developed during the first world war when several Canadians served at the Mount Vernon and Colchester heart hospitals, where under the direction of Lewis and with the help of Mackenzie the effort syndrome was investigated. Thomas Cotton and Jonathan Meakins both returned to Britain after the war, Cotton to join the staff of the National Heart Hospital in due course. His portrait hangs outside the Osler Room of the Royal College of Physicians, which he had endowed. Meakins became the first full time professor of medicine at Edinburgh, a post that he held until 1924 when he returned to Montreal to become the first chief of the full time staff at the Royal Victoria Hospital.

Segall's own contributions deserve wider knowledge. He graduated from McGill in 1920 and worked with Maude Abbott and later in Boston with Paul Dudley White. Subsequently he spent two years at University College, London, under Starling, working mainly with G V Anrep on the regulation of the coronary circulation. Later he went to Vienna to study under Wenckebach; before returning to North America he also visited Vaquez and Clerc in Paris. He rapidly became a key figure in Canadian cardiology and one of the founders in 1947 of the Canadian Cardiovascular Society, and has also been its archivist for the last quarter century. It is a tribute to him that he has assembled these data that provide us with knowledge of how Canadian cardiology developed.

DENNIS M KRIKLER

Br Heart J 1989;62:80

Notices

British Cardiac Society

The Annual General Meeting will take place in Torquay on 22 to 25 May 1990.

Paediatric cardiology

The Third World Congress of Pediatric Cardiology will take place in Bangkok on 26 November to 1 December 1989. For further information contact The Secretariat, Chulalongkorn Hospital, PO Box 48, Bangkok 10500, Thailand.

Atrial arrhythmias

A meeting on Current Concepts in the Study and Management of Atrial Arrhythmias will be held in Lyon on 6 to 8 December 1989. For further information write to PMV Congres/Arythmies 89, 130 rue de Clignancourt, 75018 Paris, France.

Ambulatory monitoring

The Fourth International Symposium on Ambulatory Monitoring will be held in London on 28 and 29 May 1990. For further information write to Ambulatory Monitoring Secretariat, Academic Cardiology, Freeman Hospital, Newcastle upon Tyne NE7 7DN.

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Chemical shift magnetic resonance imaging of human atheroma

R H MOHIADDIN, D N FIRMIN, S R UNDERWOOD, A K ABDULLA, R H KLIPSTEIN, R S O REES, D B LONGMORE

From the National Heart and Chest Hospitals, London

SUMMARY Fifteen necropsy specimens of human descending aorta and from eight patients with atheromatous vascular disease were studied by magnetic resonance imaging at 0·5 T. Images were acquired in coronal and transverse planes to localised protruding lesions and then chemical shift imaging was performed by techniques described by Dixon and by Hinks. These techniques produce images in which signal strength is proportional to lipid content. The signal was expressed as a percentage of that from extravascular fat. The total lipid content and its distribution within the plaques were noted. After imaging, the postmortem specimens were examined histologically and the lipid content of the plaque was assessed on a semiquantitative scale. The distribution of lipid within the plaque and between intima and media was also noted. The findings of chemical shift imaging agreed well with histological examination both for total lipid content and for distribution within each plaque. Chemical shift imaging also provided an assessment of the lipid content of the plaques measured in living patients, but validation was more difficult. The usefulness of the technique in routine clinical practice remains to be established.

Atherosclerotic arterial disease is the commonest cause of death and disability in Europe and North America. Its pathogenesis is controversial[1 2] but various lesions affect the arterial wall—from non-protruding fatty streaks to more complex lesions consisting of lipid, smooth muscle, and fibroblasts, which are occasionally calcified. A widely applicable technique for the detection and classification of atheroma will provide not only a method of detecting and monitoring the disease at an early stage, but also a method studying its development and response to intervention.

Conventional magnetic resonance imaging is able to show atheromatous lesions in postmortem human arteries,[3] in animal models,[4] and in patients with atherosclerosis.[5 6] Most studies, however, have relied upon distortion of the arterial lumen and have not used direct visualisation of the atheroma. Those that have, have used conventional techniques that image hydrogen irrespective of the chemical environment, and have not exploited the chemical shift of resonant frequency between the hydrogen in water and that in fat (3·3 parts per million). When nuclei with only one resonant frequency are imaged rather than the entire spectrum of resonant frequencies the technique is called chemical shift imaging.[7 8] With these techniques magnetic resonance should be able to detect atheroma non-invasively and to classify it according to its lipid content.

Our aim was to show the potential of magnetic resonance chemical shift imaging in postmortem specimens and in living patients. We used two different chemical shift imaging techniques. The method of Dixon gives an image in which pure water and pure fat produce no signal and tissues with a mixture of water and fat have higher signal.[9] The method of Hinks and Quencer is a true water or fat imaging technique where only signal from water or from fat contributes to the image.[10]

Patients and methods

METHODS

We used a Picker International Vista MR2055 machine operating at 0·5 T. To obtain conventional images we used a spin echo sequence (repeat time 1000 ms, echo time 40 ms) with two repetitions of 256 phase encoding steps for the aortic specimens

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and 128 for the clinical study. Electrocardiographically gated imaging was used to acquire end diastolic images. The slice thickness was between 5 mm and 10 mm and the field of view was between 15 cm and 25 cm as appropriate. The typical pixel dimensions of the images of the aortic specimens were 0·6 mm × 0·6 mm and of the clinical images 1·2 mm × 1·2 mm.

For the Dixon technique[9] of chemical shift imaging two images were acquired, the first with a conventional spin echo sequence with an echo time of 40 ms, and the second with a modification of the sequence where the 180° pulse was applied 3·5 ms early (16·5 ms after the 90° pulse) but the echo time remained at 40 ms (fig 1). The first sequence gives an "in phase" image, because the protons of fat and water precess with the same phase at the time of the echo and the signal is the sum of that from fat and water. The second sequence gives an "out of phase" image because the phases of fat and water protons are diametrically opposed at the time of data collection. The signal is seen in pixels containing a high percentage of water or fat, but if there is an equal amount of each, the opposing phases lead to cancellation of signal. Subtraction of the two images gives a map of the pixels containing a mixture of fat and water while pure fat and pure water give no signal.

In the Hinks technique,[10] a modified spin echo sequence is used and a narrow bandwidth 90° radiofrequency pulse is applied in the presence of a slice selection gradient. Since the resonant frequencies of water and fat differ, those from the excited slice of water and of fat are offset from each other in space. The offset as a fraction of slice thickness is equal to the chemical shift divided by the pulse bandwidth, and if the pulse bandwidth is less than the chemical shift the two slices do not overlap. The 180° radiofrequency pulse is applied in the presence of an opposite slice selection gradient, so that the slices of water and fat experiencing this pulse are offset in the opposite direction. The position of the slices can be adjusted so that only fat or only water

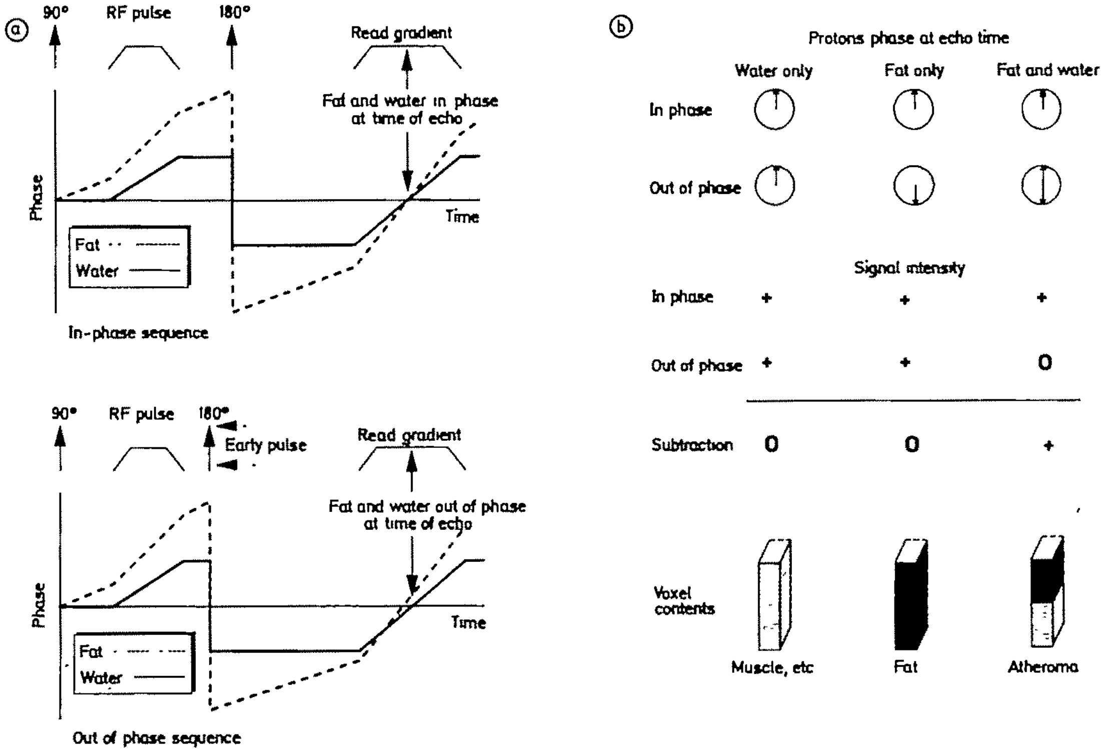

Fig 1 *Diagram of pulse sequences. (a) A conventional spin echo sequence with an echo time of 40 ms gives an in phase image because fat and water precess with the same phase at the time of the echo and the signal is the sum of that from fat and water. The second sequence is a modified asymmetrical spin echo sequence that gives an out of phase image in which the signal is the difference of that from fat and water. (b) The phase of fat and water protons differs at the time of image acquisition in the "in phase" and "out of phase images". Subtraction of the two images results in signal only from voxels containing both fat and water.*

experience both radiofrequency pulses and so only fat or only water give a signal.

Experimental calibration of the chemical shift images was performed by scanning a tube containing unmixed oil and water with a 20 mm thick slice parallel to the interface between the two. The proportion of oil and water was varied by moving the slice to contain more or less oil. The signal produced by the chemical shift imaging techniques could therefore be studied as a function of the proportion of oil present.

PATIENTS

Specimens of the descending aorta obtained at necropsy were distended with air at 80 mm Hg pressure and scanned in a chamber maintained at 37°C. A surface coil was used and a coronal image was first obtained followed by transverse images through areas with suspected atheroma. The Dixon method was used and signal strength in the subtraction image was expressed as a percentage of signal strength from extravascular fat.

After the scan, the aorta was opened to confirm the presence of atheroma and histological examination was performed with haematoxylin and eosin, elastic Van Gieson, and oil red O stains. Lipid deposition within the plaque was assessed by a pathologist, who was unaware of the magnetic resonance findings, using a semiquantitative scale from 0 to 3, where 0 corresponded to no lipid deposition and 3 to heavy deposition.

We also studied two patients with coronary artery disease and six with peripheral vascular disease. Atheromatous plaques within the thoracic and abdominal descending aorta were located by spin echo imaging. The Dixon method of chemical shift imaging was used to measure the proportion of lipid within the plaques by comparison of the signal strength with that from extravascular fat.

Results

Figure 2 shows the results of the experimental calibration of the Dixon method of chemical shift imaging. The signal strength in the subtraction image was plotted as a function of the proportion of oil, and a maximum signal was obtained with a 50% mixture of water and fat as expected. Pure water and pure fat gave a relatively low signal.

The table shows the correlation between histological grading of lipid within 10 atheromatous lesions and the signal intensity in the lesions in the Dixon subtraction image. There is a relation between the two, with the three plaques with lowest signal (8%, 8%, and 14%) having absent or little lipid (grade 0 and 1), and the other plaques with signal intensity >25% having moderate or high lipid content (grade 2 and 3).

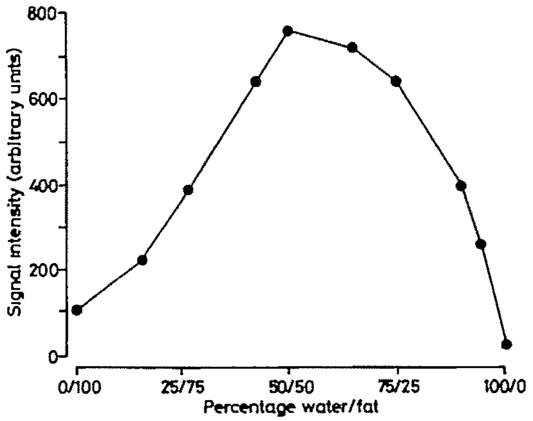

Fig 2 *Chemical shift imaging of a phantom containing different proportions of oil and water. The signal strength in the subtraction image is displayed as a function of the percentage of oil. A maximum signal was obtained with a 50% mixture of water and fat as expected, whereas pure water and pure fat gave relatively low signals.*

Figure 3 shows a lipid rich atheromatous plaque in a postmortem aorta. The in phase magnetic resonance image shows both the plaque and an area of extravascular fat. The subtraction image shows relatively high signal within the plaque (45% of signal from extravascular fat), indicating a high lipid content. This was confirmed histologically by grade 3 lipid deposition.

Lipid deposition within the plaques was not uniform. Figure 4 shows a plaque with mainly intimal lipid. This was shown by the magnetic resonance images and confirmed histologically.

Figure 5 shows a lipid deficient plaque. There is very low signal in the subtraction image within the plaque, and the histological grading was 0.

Figure 6 shows an oblique section perpendicular to

Table *Signal strength from the area of atheroma in the subtraction image of the Dixon technique (expressed as a percentage of signal from extravascular fat) compared with the histological grading of lipid deposition with the plaque*

Plaque number	*Signal (%)*	*Histology*
1	8	0
2	8	0
3	14	1
4	33	2
5	50	3
6	45	3
7	30	3
8	30	3
9	26	3
10	25	3

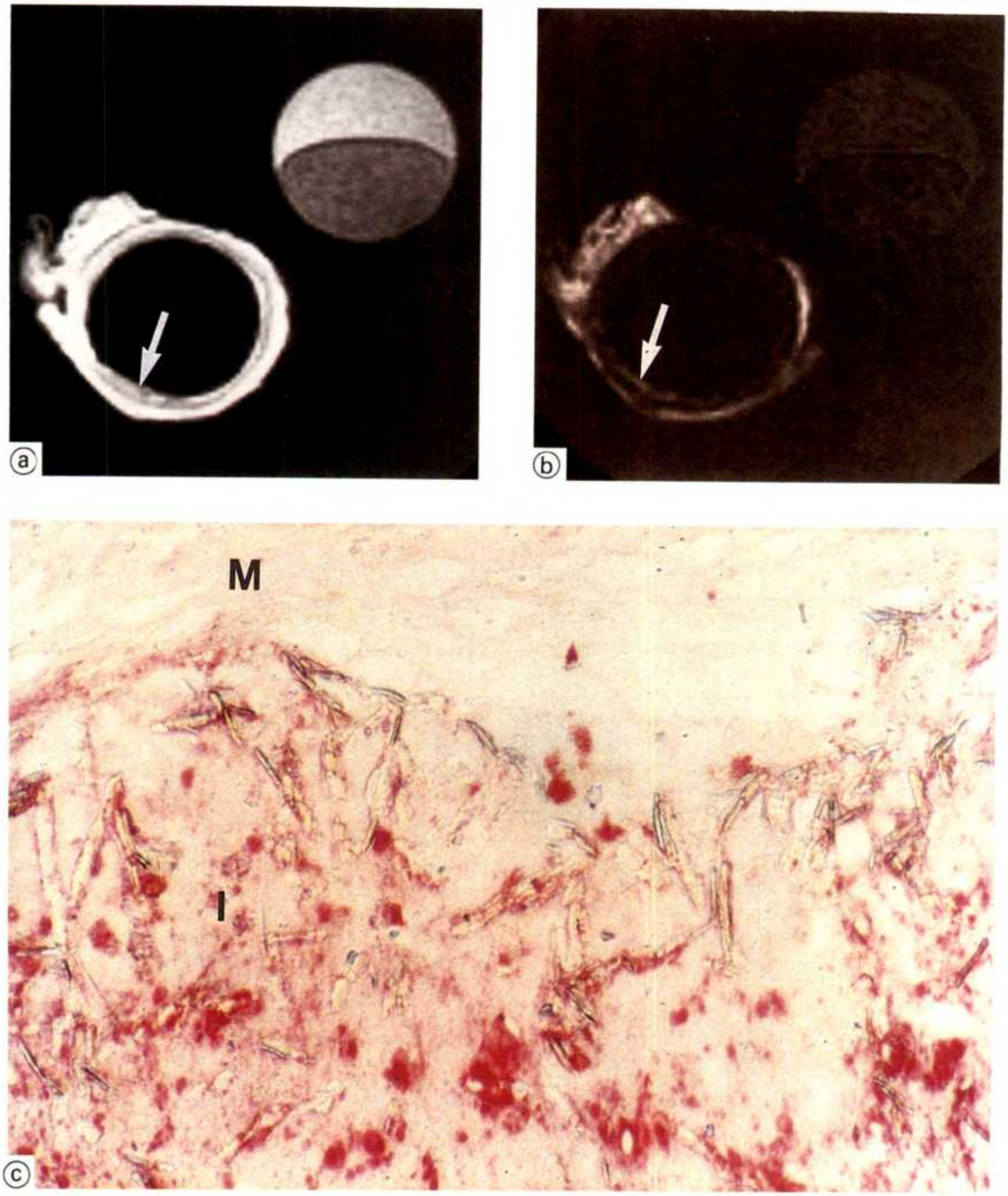

Fig 3 *(a) Postmortem aortic specimen imaged by a conventional spin echo sequence together with a phantom containing oil floating on water. Atheroma affected approximately half of the circumference of the vessel and the largest accumulation is arrowed. (b) The subtraction image shows high signal in extravascular fat and in the lesion. The ratio of signal intensity compared with extravascular fat is 45%. The oil and water in the phantom give low signal as expected. (c) Histology of the same plaque (oil red O stain) showing grade 3 lipid deposition (red) within the intima (I) and media (M).*

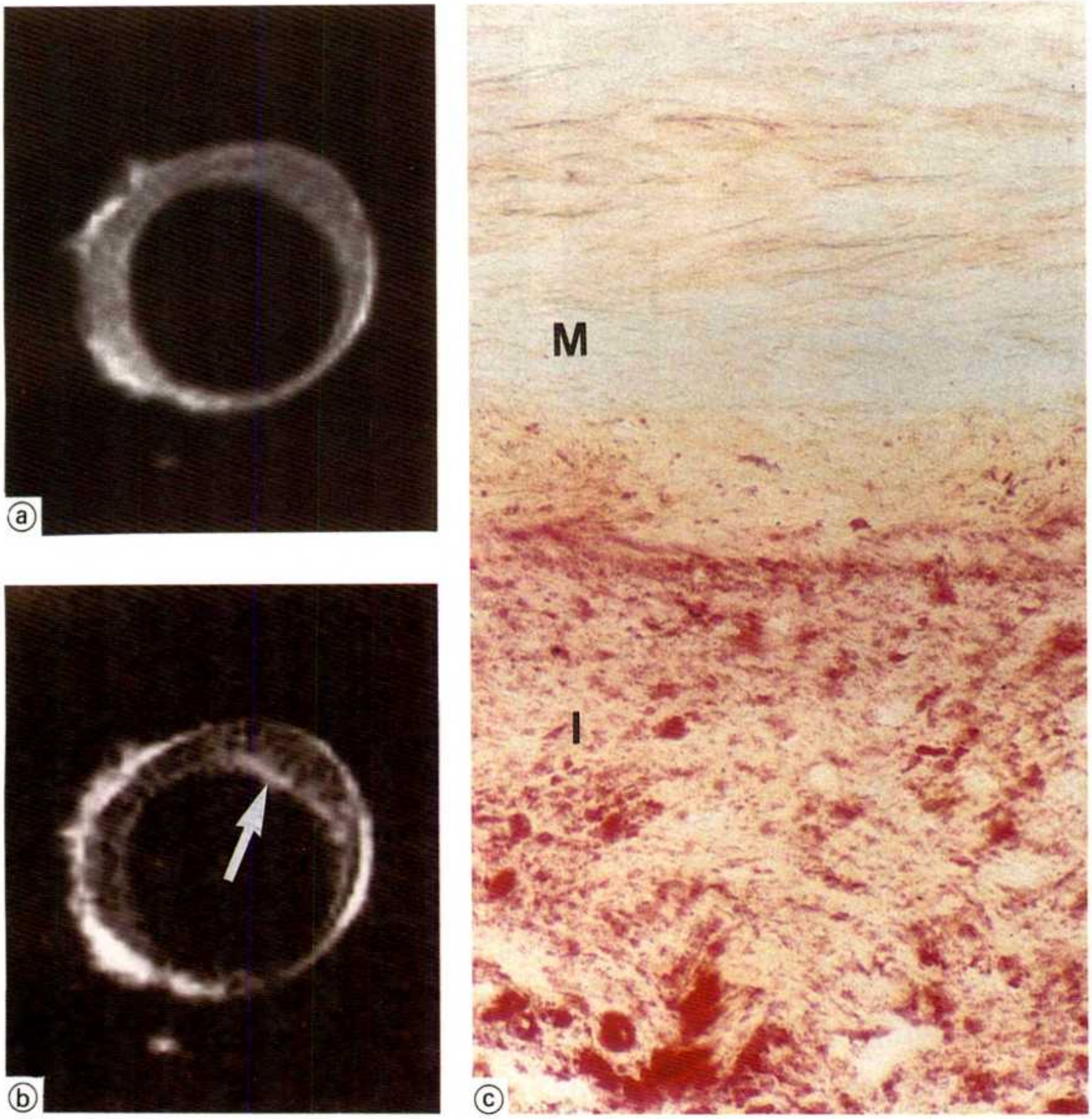

Fig 4 *(a) Atheroma affected 70% of the circumference of this aortic specimen. (b) The subtraction image shows high signal (33% of extravascular fat) limited to the intima in one location (arrowed). (c) Histology of the same plaque showing grade 3 lipid deposition (red) limited to the intima (I).*

the descending abdominal aorta in a 60 year old man with peripheral vascular disease. The circular lumen is distorted by thickening of the wall corresponding to an atheromatous plaque. The subtraction image shows a low signal within the plaque indicating a low lipid content. End diastolic images were found to be more useful than systolic images for definition of the vessel wall, because at this phase of the cardiac cycle blood is moving relatively slowly and gives high signal and good contrast with the wall.

Figure 7 shows another plaque in a 57 year old man with peripheral vascular disease. There is high signal

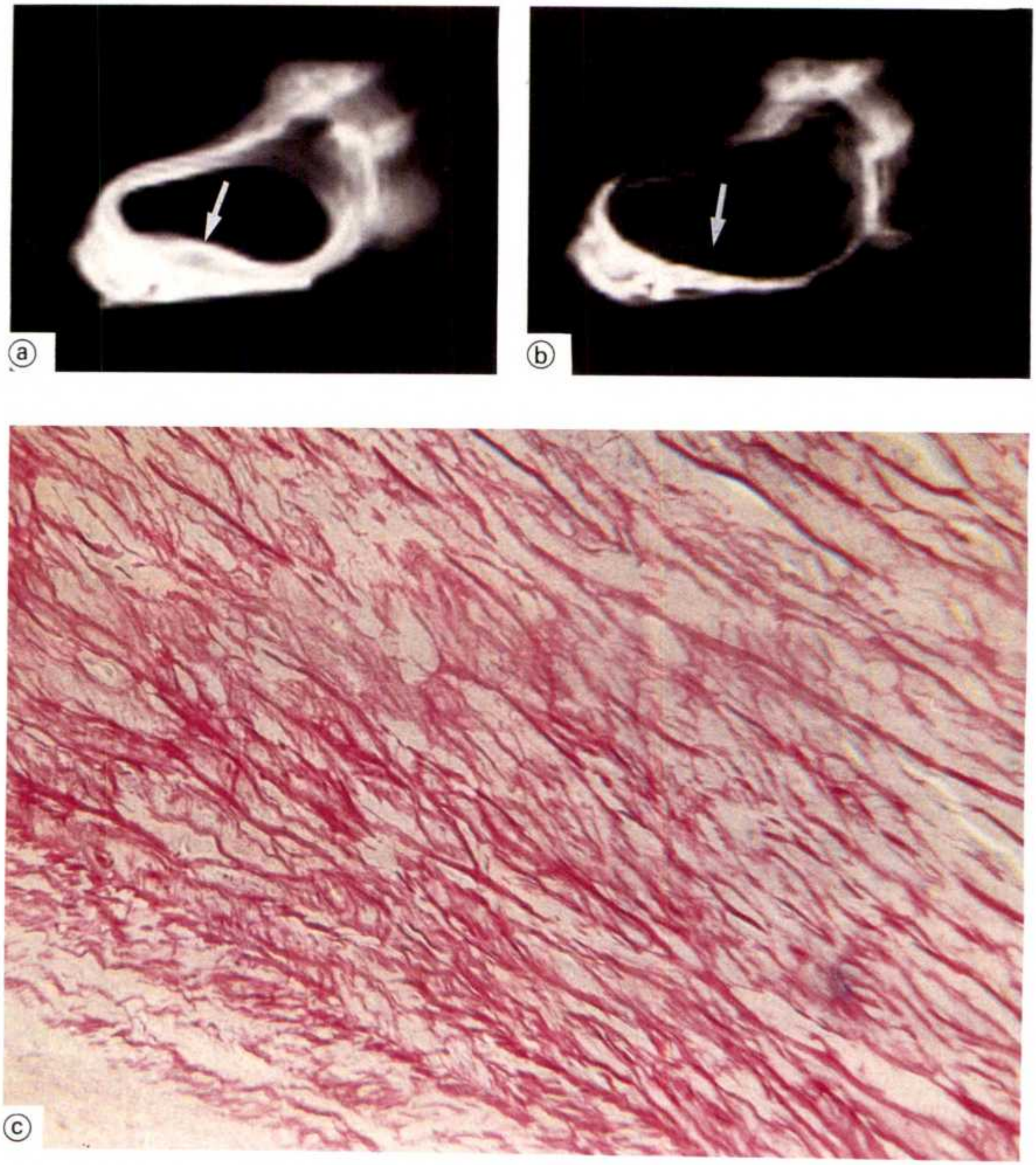

Fig 5 *(a) Conventional image of a lipid deficient plaque in a postmortem aortic specimen (arrowed). (b) The subtraction image shows very low signal (8%) compared with that from the extravascular fat. (c) Elastic Van Gieson stain of the same plaque indicates a predominantly smooth muscle and fibrous plaque. Lipid deposition would appear as vacuoles in this alcohol treated stain, but there are none.*

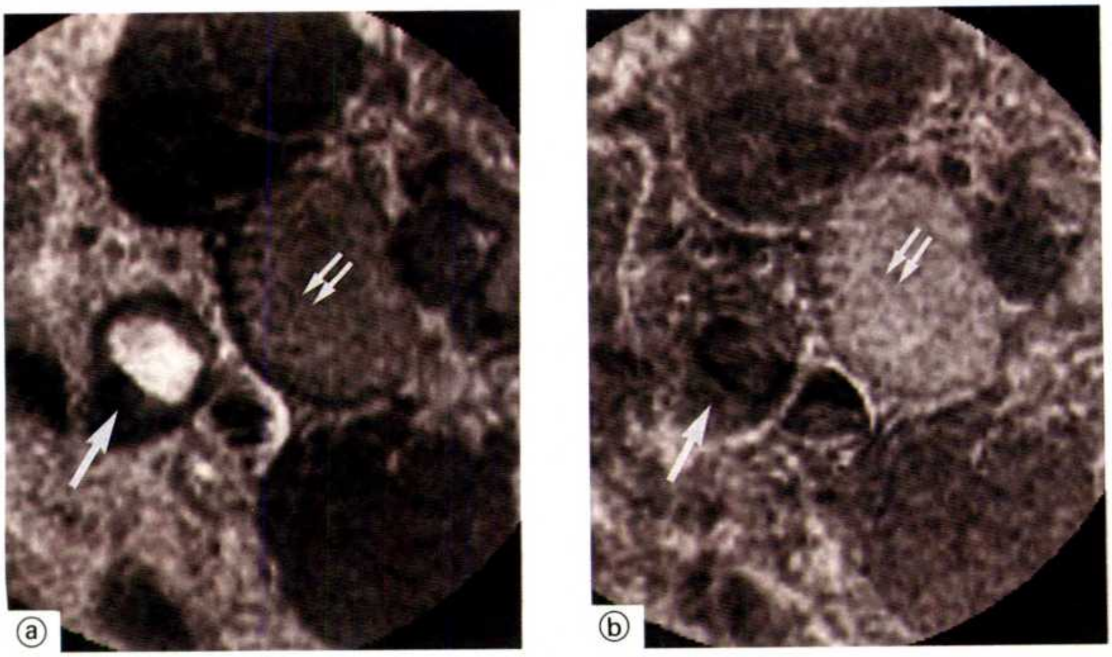

Fig 6 *(a) Spin echo image perpendicular to the descending aorta of a 60 year man with peripheral vascular disease, showing a large atheromatous plaque expanding the vessel wall (arrowed). (b) The subtraction image shows low signal in the lesion (arrow) indicating low lipid content. There is high signal from extravascular fat and from the bone marrow in the body of the lumbar vertebra (double arrow).*

in the subtraction image, indicating a high lipid content.

Figure 8 shows an example of the Hinks method of chemical shift imaging. A postmortem aortic specimen with atheromatous lesions was scanned together with a phantom of oil and water. The technique produces true fat and true water images, in contrast with the Dixon technique which produces high signal from mixtures of fat and water. This is apparent from the phantom. In the specimen, a high signal is seen in the extravascular fat in the fat image but almost no signal from lipid within the vessel wall.

Discussion

We showed that it is possible to use the chemical shift between protons in lipid and in water to acquire magnetic resonance images in which signal strength depends upon lipid content. Theory predicts that, with the use of the Dixon technique, a maximum signal will be obtained in the subtraction image from an equal mixture of lipid and water, and that low signal will be obtained from pure water and from pure fat. The theory is complex, however, and it is difficult to predict the exact shape of the curve because the signal strength is strongly dependent upon the imaging variables and upon the relaxation times of water, fat, and their mixtures. Nevertheless, we showed a maximum signal from an equal mixture of oil and water, and we were able to use the signal strength from extravascular fat as a standard. An unexpected finding was that extravascular fat gave a high signal, implying that there was a mixture of fat and water in "pure" fat. This may be explained by the presence of connective tissue and other non-lipid cellular components.

Since the shape of the relation between signal strength and fat content has a maximum, any single measurement of signal could correspond to two proportions of fat. It might therefore be difficult to know whether a plaque with low signal contains either pure fat or pure water, and unless the proportion of lipid is always either one side or other of the maximum, ambiguities could arise. In practice this is not the case because even the most lipid rich plaques have a relatively low fat content. The percentage of intimal and medial lipid in atheroma varies with different types of lesions; in the fatty streak, for example, it is 8% while in the porridge type it is

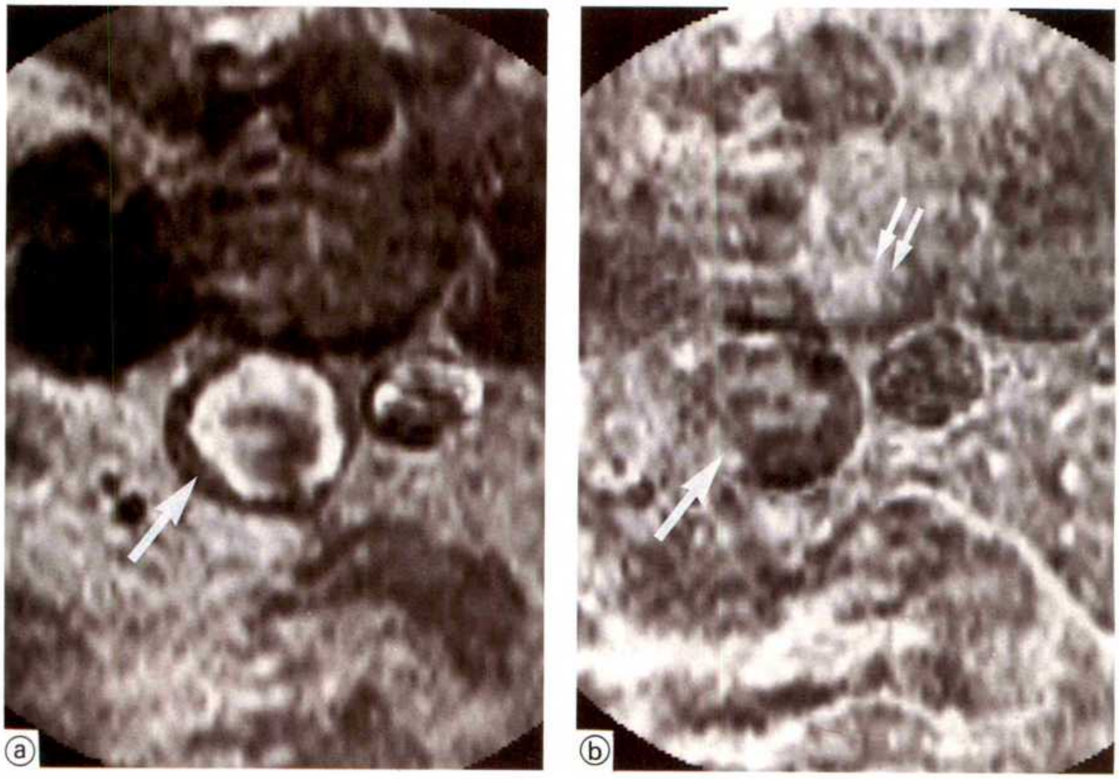

Fig 7 *(a) Spin echo image perpendicular to the descending aorta of a 57 year man with peripheral vascular disease. The wall is irregularly thickened with atheroma and the main accumulation is arrowed. The subtraction image (b) shows high signal within the lesion indicating high lipid content (similar to the marrow in the lumbar vertebral body (double arrow)).*

18%,[11] but it is reasonable to equate an increasing signal with increasing lipid content.

The shape and composition of arterial segments containing atheroma are of considerable importance. Plaques of different shape (concentric or eccentric for example) have different effects on the arterial wall in terms of their potential for thrombosis and arterial spasm.[12] The lipid content may also affect the propensity for fissuring, ulceration, and thrombosis.[13] Other properties of atheroma that may be affected by the lipid content are the short term and long term outcome of angioplasty and the potential for regression. Although little is known of these areas it is possible that there is a link between the composition of atheroma and its susceptibility to mechanical or chemical intervention. There is certainly evidence of regression in laboratory animals and that it may be possible to alter the rate of progression in man.[14–16]

Although most of our studies were in postmortem specimens we showed the feasibility of using chemical shift imaging to study atheroma in living patients. This application is difficult and there are several factors which need careful attention. Motion artefact could be a problem and if a signal is obtained from moving blood it may produce noise on the image and either mimic or obscure areas of atheroma. We did not find this to be an important problem and we preferred to acquire images at end diastole, when the relatively slowly moving blood gave a high signal that aided the delineation of the vessel wall. A second problem is that accurate registration is important in any technique that uses subtraction of images. The patient must not move between acquisition of the two images of the Dixon technique, although with suitable modifications to the scanner it should be possible to interleave acquisition of the two images so that they are acquired at the same time.

Another factor influencing the ease of chemical shift imaging is magnetic field strength. The absolute chemical shift (in Hz) depends upon the field strength and in the Hinks technique greater separation is obtained between the water and fat slices at

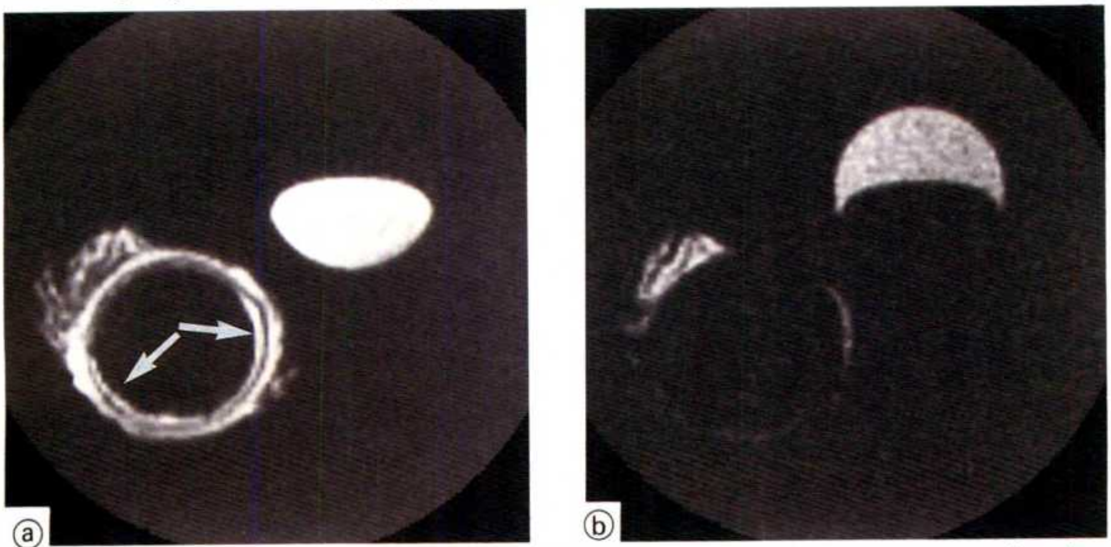

Fig 8 *True fat and true water images acquired by the Hinks technique. (a) In the water image, a postmortem aortic specimen lies beside a phantom containing oil floating upon water, but only the water is seen. The vessel wall is thickened by atheroma for 60% of its circumference (arrowed). (b) The fat image shows high signal from the extravascular fat, but low signal from the areas of atheroma, and in the phantom only the oil is seen.*

higher field strengths. High field strength would therefore make the technique more reliable for static specimens, but it may produce more motion artefact in patients.

Magnetic resonance imaging provides a method of assessing the site, size, and shape, as well as the lipid content of atheromatous plaques. Validation in vivo is more difficult than in vitro but images were obtained. The utility of the technique in routine clinical practice remains to be established.

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Regional aortic compliance studied by magnetic resonance imaging: the effects of age, training, and coronary artery disease

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SUMMARY Arterial compliance was measured in 70 healthy volunteers, 13 athletes, and 17 patients with coronary artery disease. Magnetic resonance images were acquired at end diastole and end systole through the ascending aorta, the aortic arch, and the descending thoracic aorta. Regional compliance was derived from the change in luminal area in a slice of known thickness and from the pulse pressure. Total arterial compliance was also measured from the left ventricular stroke volume and the pulse pressure. In the volunteers, mean (SD) regional compliance (μl/mm Hg) was greatest in the ascending aorta (37 (18)), lower in the arch (31 (15)), and lowest in the descending aorta (18 (8)), and it decreased with age. Compliance in the athletes was significantly higher than in their age matched controls (41 (16) versus 22 (11) μl/mm Hg). In the patients with coronary artery disease it was significantly lower (12 (4) *v* 18 (10)) than in age matched controls. Total arterial compliance also fell with age in those with coronary artery disease although there was more variation.

The results suggest a possible role for compliance in the assessment of cardiovascular fitness and the detection of coronary artery disease.

A popular saying is that a man is as old as his arteries. The commonest arterial disease is "hardening of the arteries" or atherosclerosis which leads, among other things, to a loss of elasticity. Arterial elasticity is measured as compliance, which is the change in volume per unit change in pressure, and compliance measurements may be valuable for both detection and monitoring of disease.

Magnetic resonance imaging is a direct non-invasive way of studying regional aortic compliance and total arterial compliance. We used it to study changes in compliance with age and aortic compliance in athletes and in patients with coronary artery disease.

Patients and methods

We studied 70 healthy volunteers without symptoms of cardiovascular disease (mean age 38, range 16–83), 13 athletes (mean age 43, range 29–56), and 17 patients with coronary artery disease without previous infarction (mean age 53, range 30–76). Three of the athletes were of international standard (one Olympic gold medal) and the others were club athletes. The average distance run daily was nine miles.

We used a Picker International Vista MR2055 machine operating at 0·5 T to acquire images at end diastole and end systole in three oblique planes perpendicular to the midpoints of the ascending aorta, the aortic arch, and the descending thoracic aorta (fig 1). A spin echo sequence (TE 40 ms) was used with two averages of 128 phase encoding steps, a pixel size of 1·17 mm × 1·17 mm, and a slice thickness of 10 mm. The end diastolic images were acquired 100 ms before the average RR interval, and the end systolic images at the end of the T wave of the electrocardiogram Acquisition time was three to four minutes per image depending upon heart rate.

The lumen of the aorta was outlined manually on the computer screen, and regional aortic compliance was calculated from the change in volume between diastole and systole. The pulse pressure was

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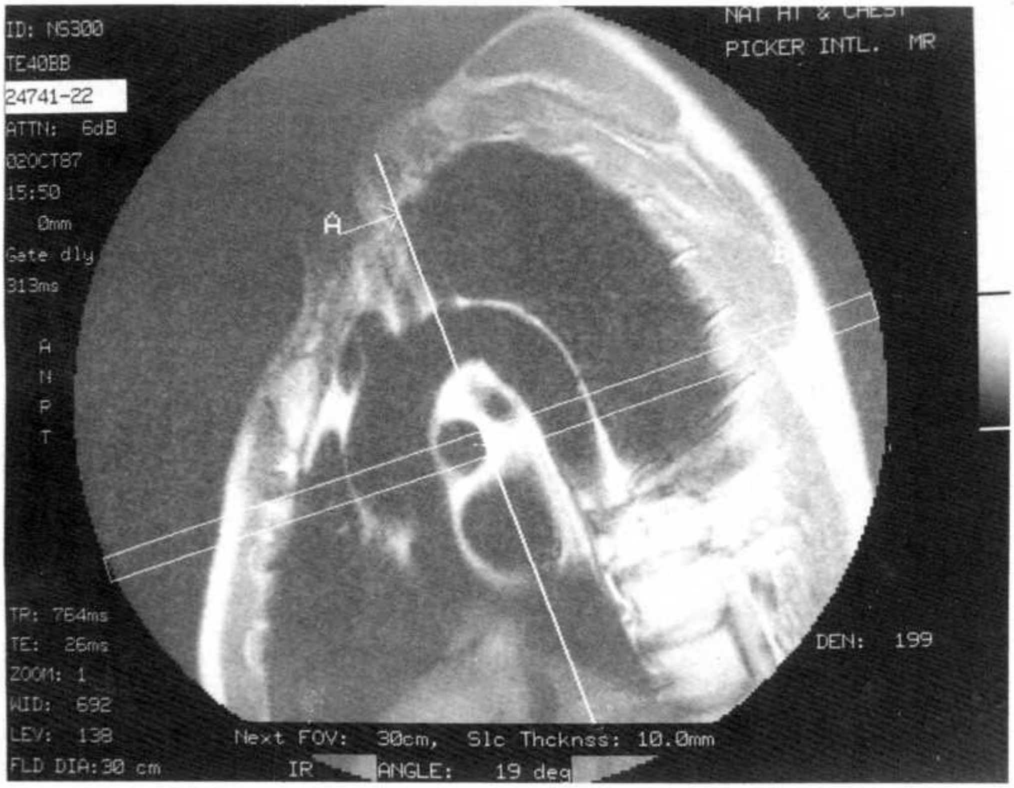

Fig 1 *Oblique image of the ascending aorta, aortic arch, and descending thoracic aorta showed the sites at which compliance was measured.*

measured with a conventional sphygmomanometer. Left ventricular end diastolic and end systolic volumes were calculated from biplane area-length measurements in the horizontal and vertical long axis planes,[1] and total arterial compliance was derived from the left ventricular stroke volume and the pulse pressure.

We used the unpaired Student's *t* test to test the differences between groups, and used a correction for multiple comparisons for comparisons between sites.[2] Normal ranges for compliance were derived from the 95% confidence intervals of the linear regression lines in figs 3–5. Linear regression was performed after logarithmic transformation because the relation between compliance and age was curved.

Results

Figure 2 shows images at end diastole and end systole through the ascending and descending aorta in a volunteer aged 38. The mean (SD) percentage change in ascending aortic area in volunteers aged less than 50 was 30 (13)%, which was significantly greater than the known reproducibility of area measurements by this technique (6%).[3]

Mean (SD) regional compliance measurements in the healthy volunteers (mean (SD) age 37) were (30·9 (15·3)) in the ascending aorta, 21·4 (10·7) in the aortic arch, 17·8 (8·3) in the descending aorta, and total arterial compliance was 1854 (489) (μl/mm Hg). Mean compliance in the ascending aorta was higher than in the arch ($p < 0·01$ by the multiple comparison test) and in the descending aorta ($p < 0·01$). The

Table 1 *Mean regional compliance (SD) in patients with coronary artery disease and athletes compared with age matched volunteers. The values are the means of each site in all the subjects in each group*

	Age	*Compliance*
Age matched volunteers	47 (11)	17·6 (10·3)
Patients with coronary artery disease	53 (11)	11·6 (4·0)**
Age matched volunteers	41 (9)	21·8 (11·2)
Athletes	47 (7)	41·0 (16·2)***

**$p < 0·01$, ***$p < 0·001$.

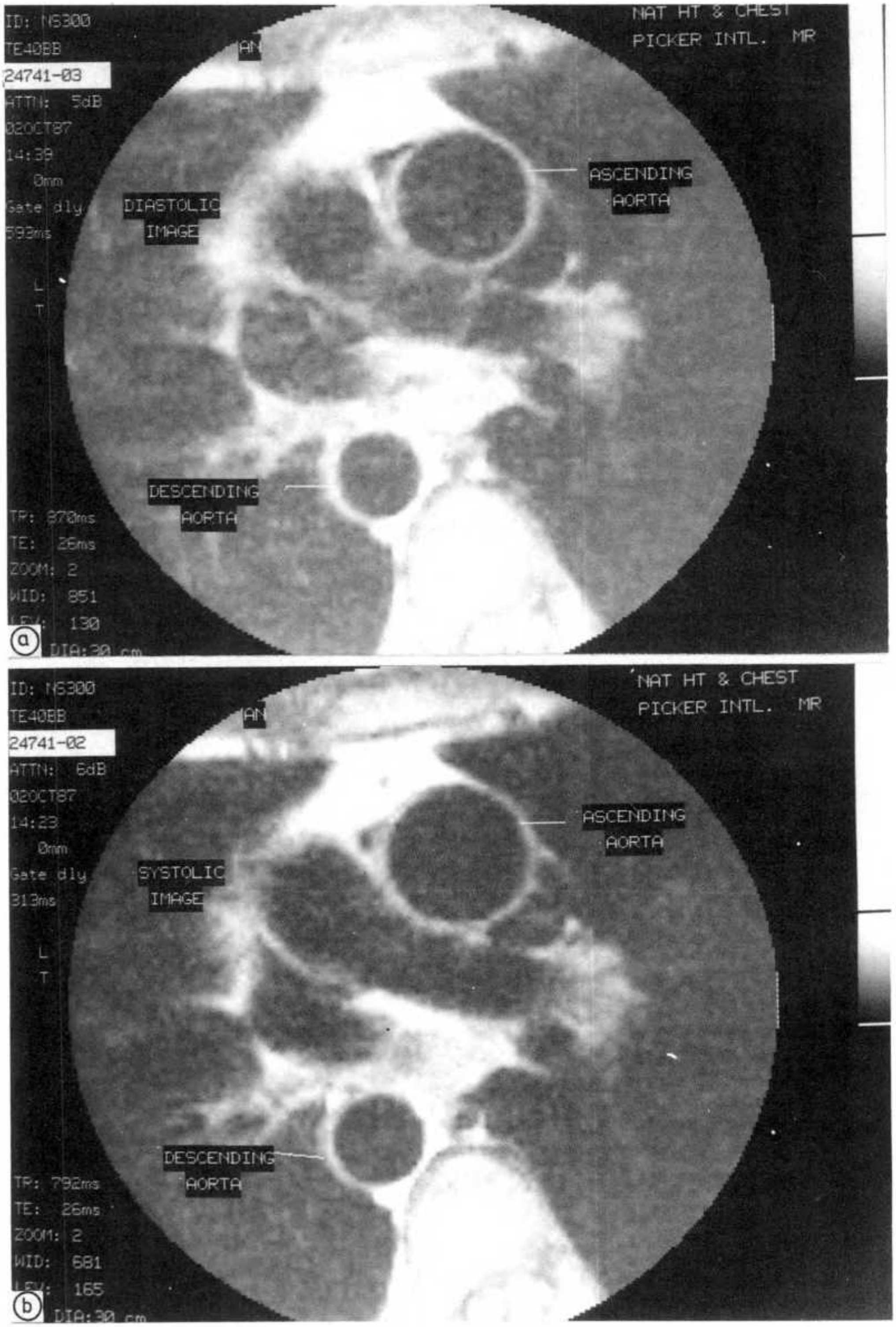

Fig 2 *Diastolic (a) and systolic images (b) of the ascending and descending aorta showing the change in aortic area of a 38 year old normal volunteer.*

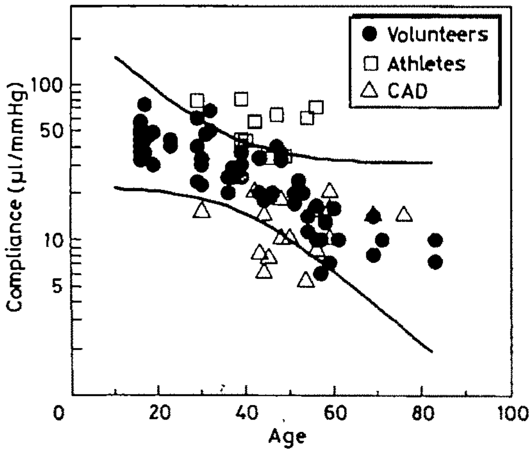

Fig 3 *Compliance in the ascending aorta displayed on a logarithmic scale and plotted against age. The regression equation is* $y = -0\cdot01\,x + 1\cdot79$, *and the 95% confidence intervals for the normal volunteers are shown* ($r = -0\cdot91$, $p < 0\cdot001$, *SEE* $= 0\cdot09$).

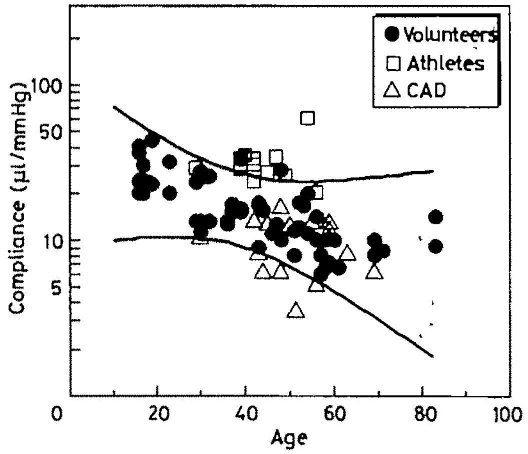

Fig 5 *Compliance in the descending aorta displayed on a logarithmic scale and plotted against age. The regression is* $y = -0\cdot008\,x + 1\cdot5$, *and the 95% confidence intervals for the normal volunteers are shown* ($r = -0\cdot74$, $p < 0\cdot001$, *SEE* $= 0\cdot14$).

difference in compliance between the arch and the descending aorta was not significant (p > 0·05).

Mean compliance in the athletes and in the patients with coronary artery disease was compared with age matched volunteers. Compliance was significantly higher in the athletes and lower in the patients with coronary artery disease than in their age matched controls (table 1).

Figures 3–5 show the relation between compliance and age in all those studied. Compliance fell with age in the volunteers and after logarithmic transformation the fall seemed to be linear. The 95% confidence intervals of the linear regression equations were used to define a normal range. All but three athletes had compliance above the normal range at each site. Of the patients with coronary artery disease who were aged <50, most had abnormally low compliance in the ascending aorta, aortic arch, and descending aorta. Mean compliance in the patients with coronary artery disease was abnormally low, and inspection of the figures showed that the difference was most pronounced in patients aged <50. Compliance was high in the controls aged >50. Total arterial

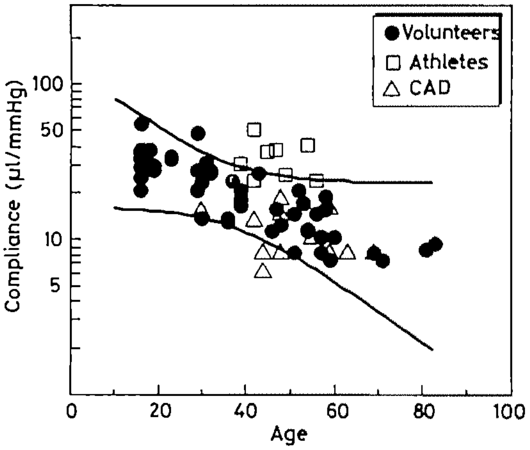

Fig 4 *Compliance of the aortic arch displayed on a logarithmic scale and plotted against age. The regression equation is* $y = -0\cdot01\,x + 1\cdot65$ *and the 95% confidence intervals for the normal volunteers are shown* ($r = -0\cdot84$, $p < 0\cdot001$, *SEE* $= 0\cdot12$).

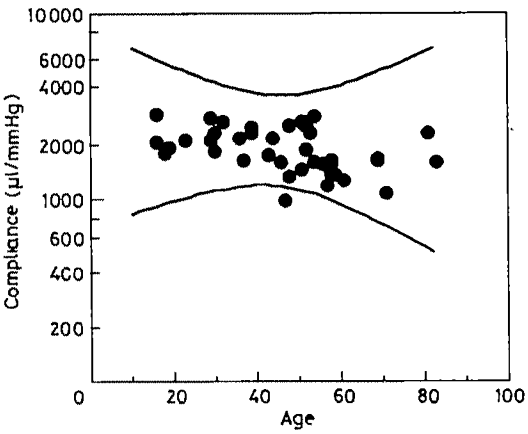

Fig 6 *Total arterial compliance in the normal volunteers plotted against age. The regression equation is* $y = -0\cdot003\,x + 3\cdot39$, $r = -0\cdot42$, $p < 0\cdot02$, *SEE* $= 0\cdot11$.

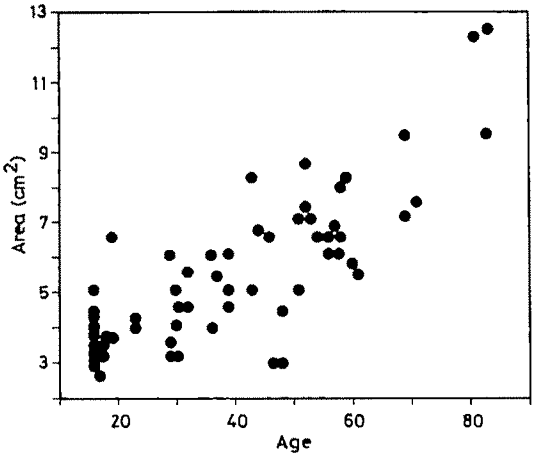

Fig 7 *Correlation between area of the ascending aorta in diastole and age ($y = 0{\cdot}09x + 2{\cdot}1$, $r = 0{\cdot}77$, $SEE = 1{\cdot}4$ cm^2).*

compliance also decreased with age in the healthy volunteers, but there was a wide scatter of points (fig 6).

Figure 7 and table 2 show the relation between diastolic aortic area and age, and fig 8 shows the change in pulse pressure with age in the healthy volunteers. Aortic size and pulse pressure both increased with age, pulse pressure mainly because of an increase in systolic pressure.

Discussion

Previous workers have measured human arterial compliance from pressure-volume curves of post-mortem arteries.[4] Arterial compliance has also been estimated in vivo by indirect and invasive techniques, including pulse wave velocity measurements in animals and in humans,[5–7] the pressure-radius relation by the Peterson transformer coil in animals,[8] x ray contrast angiography in humans,[9] and pulsed ultrasound aortography.[10] The compliance of the whole arterial system has previously been calculated from the left ventricular stroke volume divided by pulse pressure.[11] We showed that both regional aortic compliance and total arterial compliance can be measured in vivo by magnetic resonance, which is simpler and more accurate than other methods.[12]

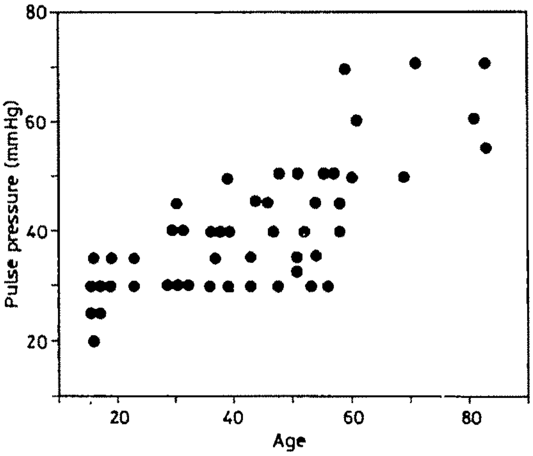

Fig 8 *Correlation between pulse pressure in the normal volunteers and age ($y = 0{\cdot}5x + 0{\cdot}5$, $r = 0{\cdot}80$, $SEE = 7{\cdot}2$ mm Hg).*

Table 2 *Mean (SD) cross sectional area of ascending aorta in each decade in the healthy volunteers*

Age (decades)	*Diastolic aortic area (cm^2)*
10–19	3·8 (0·9)
20–29	4·3 (1·1)
30–39	4·9 (0·8)
40–49	5·3 (2·0)
50–59	6·9 (0·9)
60–69	7·0 (1·8)
70–79	8·1 (0·6)
80–89	11·0 (2·9)

We showed that regional aortic compliance in healthy volunteers falls with age and is highest in the ascending aorta; this accords with studies that showed that this part of the aorta had the greatest elasticity.[13] With advancing age, there is disruption of the elastic component of the vessel wall, fibrosis and increase in collagen at the expense of smooth muscle cells, cystic medial necrosis (pooling of mucoid material), and medionecrosis (areas with loss of nuclei).[14–16] The fall in compliance with age may also be related to a deficiency of endothelium derived relaxing factor[17] or to the disappearance of peripheral β adrenergic receptors.[18] The enlargement of diastolic aortic area with age is possibly caused by the structural changes and loss of elasticity in the vascular wall. A previous necropsy study on adult human aortas showed that the enlargement of aortic diameter with age was associated with loss of elasticity.[19] Systolic blood pressure and pulse pressure increase with age.[20] A fall in arterial compliance may be one factor causing systolic hypertension,[21–23] although the structural changes seen in elderly patients with hypertension have also been reported in normotensive individuals of the same age[24] and to a lesser degree in younger subjects.[25] Decreased compliance may also lead to the decreased baroreceptor sensitivity seen in elderly patients with hypertension.[26 27] The relation between blood pressure and compliance is complex, however, because hypertension can be a cause as well as a consequence of reduced compliance.[28]

We found high regional aortic compliance in trained athletes, and it seems likely that this is due to a direct effect of training upon the arterial system, rather than its effects upon the heart. Although the bradycardia and increased stroke volume of training[29] will affect mean aortic diameter and hence compliance, there are also large changes in peripheral resistance that should have a greater effect. The reduction in resistance allows the athlete to generate a maximum cardiac output of up to 40 l/min compared with a maximum of 20 l/min in normal individuals without increasing blood pressure to unacceptable values.[30 31] These large changes in peripheral resistance may well be accompanied by structural changes in the aorta leading to increased compliance.

Because compliance is a determinant of left ventricular afterload it is important in patients with coronary artery disease.[32] The combination of elastic arteries and resistant arterioles constitutes a hydraulic filter enabling the intermittent cardiac output to be converted to a steady capillary flow. Part of the energy of left ventricular contraction produces forward flow during systole, but the remainder is stored as potential energy in the distended arteries. During diastole, elastic recoil converts this potential energy again into forward flow. A fall in aortic compliance, therefore, increases the impedance to ventricular ejection and decreases capillary blood flow.[33 34] Aortic compliance measured by aortography was reduced in patients with coronary artery disease[35] and we have now shown similar changes non-invasively. Although it is possible that this is due to the mechanical effects of atheroma, it is more likely to reflect the generalised structural changes that occur in association with atheroma and that are similar to those of aging.[36 37]

Magnetic resonance imaging is a simple non-invasive method of measuring both regional aortic compliance and total arterial compliance. In healthy volunteers, the ascending aorta was the most compliant region and compliance fell more distally. Compliance also fell with age, although above the age of 50 the fall was less steep. Regional aortic compliance is higher than normal in athletes, and lower than normal in patients with coronary artery disease. These changes are likely to be the result of structural changes in the aorta, but the importance of compliance measurements for the monitoring of cardiovascular fitness and for the detection of disease remains to be established.

We thank the Board of Governors of the National Heart and Chest Hospitals, the Coronary Artery Disease Research Association (CORDA), and Picker International Ltd, for financial support and Miss Elizabeth Burman, Mr Karl Lotey, and Miss Marjorie Watson for their assistance.

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Br Heart J 1989;62:97–101

Magnetic resonance imaging of coarctation of the aorta in infants: use of a high field strength

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SUMMARY Nineteen infants with suspected coarctation of the aorta were studied with electrocardiographically gated magnetic resonance imaging on a 1·5 T whole body imaging system. In all cases imaging was successful and produced diagnostic images of high resolution. Coarctation was shown in 12 cases. The position and shape of the coarctation were well displayed by the magnetic resonance images. In addition, they clearly showed the relation of the coarctation to arteries arising from the aortic arch and to the length and diameter of the aortic isthmus and the distal aortic arch. The anatomy was confirmed at operation in all 12 patients, except for two with a small ductus arteriosus (arterial duct), which was not seen in the magnetic resonance images. In the seven remaining patients, coarctation was excluded.

Magnetic resonance imaging produced high quality images that showed the anatomy better than other non-invasive methods. It provided all the anatomical information required for surgical correction.

Magnetic resonance has been promoted as an important advance in the imaging of congenital malformations of the heart and great vessels.[1] As yet, however, there is little evidence that it will either supplant or supplement established imaging techniques. There is no experience in very young children, the age group in which most cases of coarctation now present.[2] We report our experience of imaging the aorta in a group of infants with suspected coarctation with a high field strength magnetic resonance imaging system. The superior spatial resolution of such a system makes it particularly suitable for this age group.

Patients and methods

PATIENTS

Nineteen infants, aged between three days and 10 months, were imaged (table). In every case there was clinical or echocardiographic suspicion of coarctation of the aorta. Infants who were in severe heart failure that required intravenous inotropic support or ventilation were not included; otherwise there were no selection criteria. Four of the patients studied (patients 4, 5, 6, and 10) subsequently had aortograms. Surgical correction was performed in all the cases in which coarctation was confirmed by magnetic resonance imaging.

METHODS

The infants were fed just before the imaging procedure and, if necessary, sedated with 75 mg/kg of chloral hydrate. They were imaged by a 1·5 T whole body imaging system (Gyroscan) manufactured by Philips Medical Systems. Electrocardiogram electrodes were placed closely around the left nipple, an arrangement that minimises the distortion of the electrocardiogram produced by the movement of blood within the high magnetic field. The electrocardiogram was transmitted by a telemetry system. The infants were wrapped in a blanket and their movement was restricted by a firm foam mattress curved in a semicircle around them. They were imaged while supine in a 32 cm diameter proton head coil.

Electrocardiographically gated sections (5 mm thick), separated by 0·5 mm, were simultaneously acquired by a spin echo sequence with an echo time of

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Table *Details of patients studied*

Number	*Age*	*Anatomy shown by magnetic resonance*	*Surgical findings where different*
1	3 wk	Discrete shelf, mild isthmal hypoplasia	Small arterial duct
2	3 wk	Waist lesion, no isthmus, mild distal arch hypoplasia	Agree
3	8 days	Discrete shelf, severe isthmal hypoplasia, patent arterial duct	Agree
4	17 days	Mild isthmal narrowing, no coarctation	—
5	6 days	Discrete shelf, anomalous right subclavian artery proximal to coarctation	Agree
6	2 mnth	Anomalous pulmonary veins to coronary sinus, coarctation excluded	—
7	5 days	No coarctation	—
8	6 wk	Discrete shelf, mild isthmal hypoplasia, ventricular septal defect	Agree
9	10 mnth	Waist lesion, no isthmus	Agree
10	3 mnth	Hypoplasia of abdominal aorta, no coarctation	—
11	3 days	Normal aortic arch	—
12	3 mnth	Discrete shelf, mild isthmal hypoplasia	Agree
13	1 mnth	No isthmus, hypoplasia of distal arch, ventricular septal defect, subaortic infundibulum	Small arterial duct
14	2 mnth	Mild isthmal hypoplasia, discrete shelf, small ventricular septal defect	Agree
15	10 days	Mild isthmal hypoplasia, no coarctation	—
16	2 mnth	Severe isthmal hypoplasia, discrete shelf	Agree
17	12 days	Normal aortic arch	—
18	7 wk	Waist lesion, hypoplasia of distal arch, no isthmus	Agree
19	6 wk	Discrete shelf, distal arch and isthmal hypoplasia	Agree

30 ms. The matrix used was 256 × 256, with a typical pixel size of 0·75 mm. To reduce acquisition time we used 180 phase encoding gradients instead of the usual 256 to produce the image. Two acquisitions of each phase encoding step were averaged. This resulted in a typical scan time for one set of seven sections of about six minutes.

In every case, the initial series of sections was in the transverse plane of the body, encompassing the structures between the arch of the aorta and the diaphragm. This, typically, required seven to nine sections. Subsequent imaging planes, oblique to the standard planes of the body, were chosen to show the area of suspected coarctation. The angles for these planes, chosen individually in each patient, were determined directly from the initial series of transverse images. The most valuable imaging plane for the aortic arch was found to be an oblique sagittal, rotated around a vertical axis, to show the aortic arch (figs 1–5). Occasionally, the imaging plane had to be additionally rotated around an anterioposterior axis to show the aortic arch optimally. A coronal plane, which showed the descending aorta, was also useful in some cases.

In all the patients with coarctation, the area of narrowing was shown in the oblique sagittal plane and at least one other plane, either the transverse or coronal. In most patients it was imaged in all three planes.

Results

Images of diagnostic quality were obtained in every patient. There were no imaging failures. In all patients the electrocardiographic gating was satisfac-

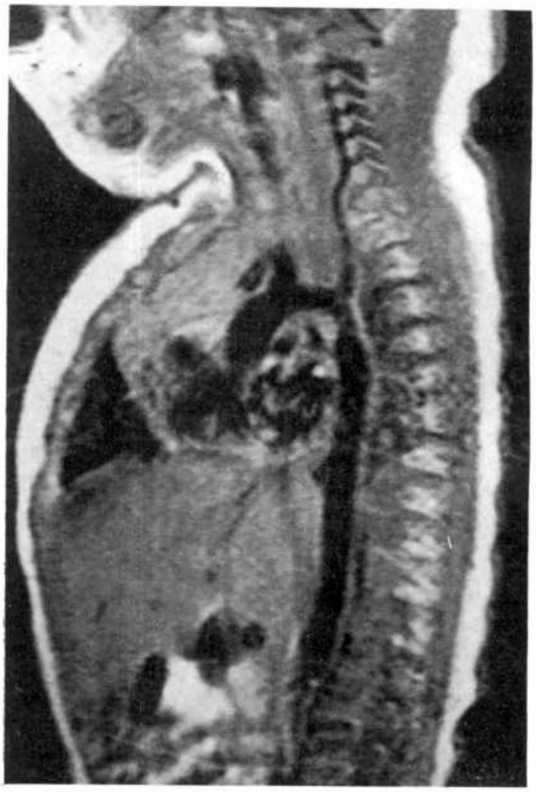

Fig 1 *A normal aortic arch in a three day old infant (patient 11). This image is in an oblique sagittal plane rotated around a vertical axis. There is some mild isthmal narrowing but no coarctation. Cross sectional echocardiography did not rule out the presence of coarctation.*

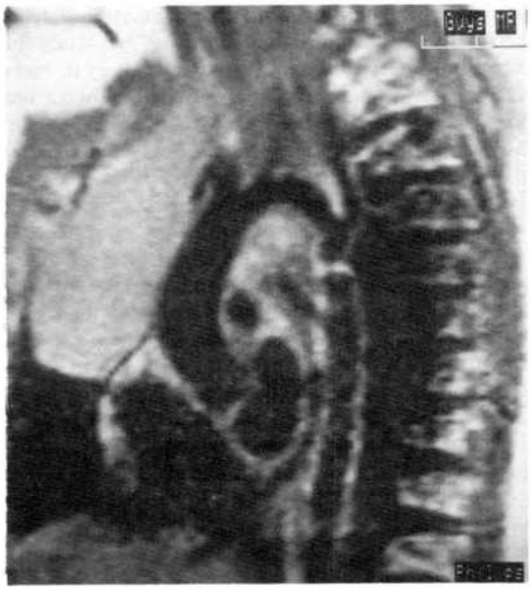

Fig 2 *An oblique sagittal section in a three month old infant with coarctation. There is a discrete shelf across the descending aorta. The length of the aortic isthmus and the relation of the coarctation to the left subclavian artery is clearly seen. There is only very mild isthmal hypoplasia.*

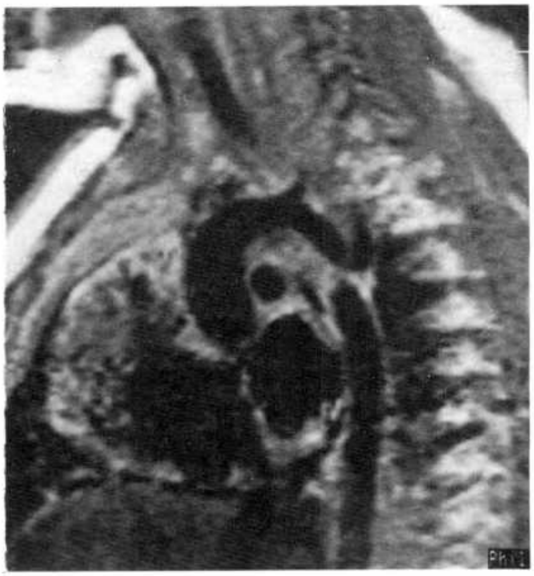

Fig 3 *An oblique sagittal section in another patient aged 10 months with coarctation. In contrast with the anatomy in figure 2, there is a waist like narrowing of the descending aorta. The origin of the left subclavian artery arises at the level of the coarctation and so there is no isthmus.*

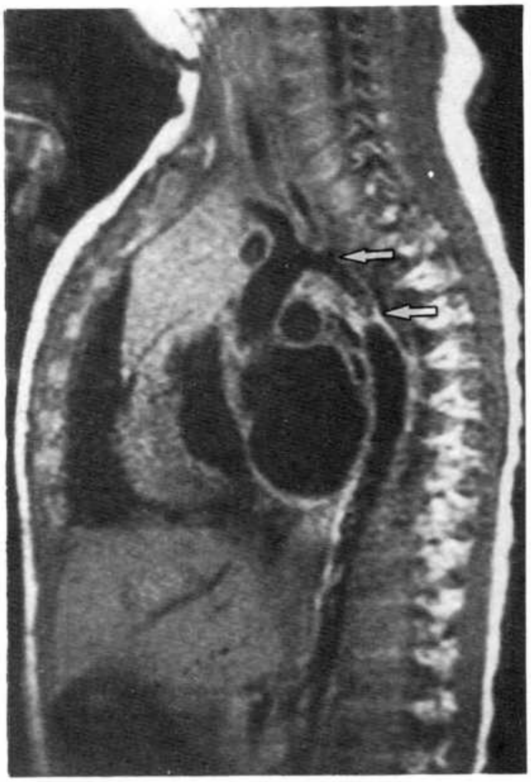

Fig 4 *An oblique sagittal section in an infant with a very long, hypoplastic isthmus (between the arrows). The coarctation forms a discrete shelf rather than a waist.*

tory. The diagnosis of coarctation was confirmed in 12 infants. It was excluded in seven. In the first case in which it was excluded (patient 4), we lacked experience in interpreting the magnetic resonance images and so the clinical picture prompted investigation by angiography. The aortogram confirmed normal aortic anatomy. In all the subsequent cases the diagnosis based on magnetic resonance imaging was accepted. Angiography was performed in two other negative cases (patients 6 and 10) to define aspects of the cardiac anatomy other than the aortic arch. In one positive case the arrangement of the branches of the aortic arch was unclear. An aortogram was performed before surgical correction to clarify this. The right subclavian artery arose anomalously just proximal to the coarctation and, in retrospect, this could be seen in the coronal images of the coarctation in this patient. In all the remaining positive cases, surgical correction was performed without further investigation.

Surgical correction confirmed the anatomy in all the patients with coarctation. But in two patients small arterial ducts (ductus arteriosus) were found at

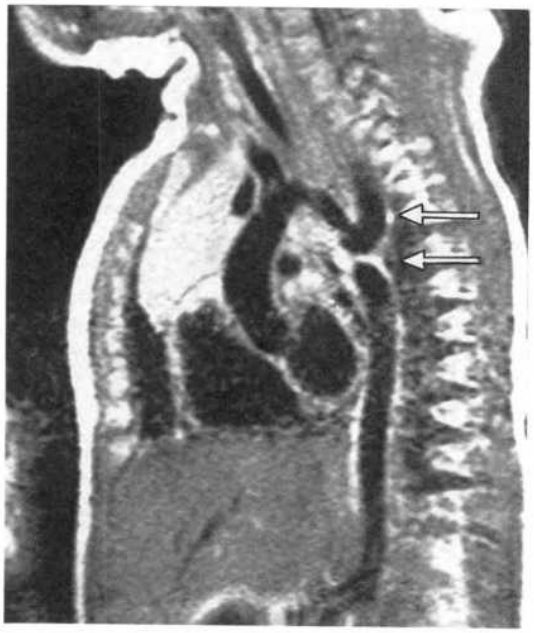

Fig 5 *An oblique sagittal section in an infant with coarctation in the form of a shelf (lower arrow). There is no isthmus and a dilated left subclavian artery (upper arrow) can be seen arising just proximal to the shelf. In this case there is considerable hypoplasia of the distal aortic arch proximal to the origin of the left subclavian artery.*

operation that were not seen in the magnetic resonance images. In practice this was not of clinical importance. In one patient a large arterial duct was shown by magnetic resonance imaging (case 3).

The presence or absence of obstruction in the thoracic aorta could invariably be shown in the initial transverse series of images. Further oblique sagittal images were, however, obtained in all cases to display the anatomy of the aortic arch clearly. From such images the diameter and length of the aortic isthmus were evident. The coarctation shelf, itself, gave a very intense magnetic resonance signal in these T1 weighted images. Images obtained in the coronal plane were valuable in defining the relation of the coarctation to the vessels arising from the aortic arch, particularly the left subclavian artery.

Discussion

To date magnetic resonance imaging of the heart has generally been performed with systems that use low and medium field strengths, $\leqslant$ 0·6 T.[3 4] It was thought that it would be difficult to achieve cardiac gating in strong magnetic fields such as 1·5 T. This is because the electrocardiographic signal is distorted by the flow of blood in the high magnetic field. But the newer, high field strength imaging systems have a potentially important advantage for the study of congenital heart disease. The signal to noise ratio from these systems is considerably better than from those that use low and medium strength fields and so a more favourable compromise between spatial resolution and imaging time can be achieved. These advantages are especially valuable when infants are studied. A major criticism of published reports is that there is almost no experience in the use of gated magnetic resonance cardiac imaging in infants. Indeed, most workers specifically avoided imaging in this age group. Because almost all patients with congenital heart disease present in the first year of life,[2] the anatomical diagnosis of cardiac defects is now generally performed in infancy. An imaging technique, to be of value, must be capable of producing high quality images in this age group.

As we have shown, magnetic resonance images can define the position of the coarctation in the aortic arch, its relation to the arterial duct and the arteries arising from the arch, the length and diameter of the aortic isthmus, and whether the coarctation is a discrete shelf or a waist lesion.[5] Identification of the coarctation is greatly helped by the intensity of the signal from the shelf itself. In infants, this is usually made up of tissue originating from the arterial duct (ductus arteriosus).[6] We always made certain that the shelf could be seen in images in at least two different planes, thus ensuring it was not an artefact produced by the oblique transection of the aorta. In practice, this does not seem to be a problem. In none of our normal patients were the appearances of the aortic arch ambiguous.

We believe that our experience shows that high field strength magnetic resonance imaging can consistently produce high resolution cardiac images in infants. In this series, we have shown that it is possible, with great clarity, to image the aortic arch. The images were of much higher resolution than those obtained with cross sectional echocardiography.[7] In addition, magnetic resonance imaging is non-invasive and safe. It does not use any ionising radiation. It provides all the anatomical information required for surgical repair of the anomaly. It thus has many advantages for studying this age group. Its clinical role requires further evaluation.

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Phase and amplitude analysis of exercise digital left ventriculograms in patients with coronary disease

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SUMMARY Phase and amplitude analysis was applied to intravenous digital left ventriculograms to avoid the artefacts associated with image subtraction. Eight controls and 40 patients with known coronary artery disease underwent digital left ventriculography before and after a symptom limited supine bicycle exercise test. The resultant images were subjected to phase and amplitude analyses. In the control group there was no deterioration in left ventricular wall motion after exercise. In 30 of the 40 patients there was a deterioration in wall motion on exercise. This group contained all eight patients with three vessel disease and 12 of the 17 patients with two vessel disease. Ten patients showed no change in wall motion—five with one vessel disease and five with two vessel disease.

Phase and amplitude analysis of digital left ventriculograms is a method of detecting exercise induced myocardial ischaemia that may help in the assessment of patients with coronary artery disease.

Digital subtraction angiography has recently been applied to left ventricular imaging to detect abnormalities of wall motion.[1 2] As in nuclear cardiology, exercise has been used to induce such abnormalities in regions rendered ischaemic by coronary stenoses, and results similar to those of nuclear gated blood pool scanning have been achieved.[3 4]

When digital subtraction angiography is performed after exercise, however, the problems of motion subtraction artefact become more important, and the image quality can be considerably impaired. This has less effect on nuclear ventriculography, where the combination of the low resolution and lack of image degradation by bone and soft tissue structures enables satisfactory imaging despite considerable cardiac motion.

We showed that satisfactory digital images of the left ventricle after exercise can be achieved by the application of an analysis technique that is not dependent on image subtraction, namely phase and amplitude analysis.[5] This has been widely used in nuclear cardiology[6 7] and may be applied to any imaging technique that acquires data in a digital format. Therefore, we decided to evaluate this technique in the assessment of patients with coronary artery disease.

Patients and methods

PATIENTS

We studied 48 patients who were investigated by coronary angiography for chest pain and suspected coronary artery disease. Eight of these patients were found to have normal coronary arteries or minor coronary disease (no coronary stenosis $>70\%$) and were used as a "control" group. Of these none had had a myocardial infarction and five were taking antianginal medication (β blockers in two).

The remaining 40 patients had angiographically significant coronary artery disease. Eighteen patients had suffered previous myocardial infarction and 36 were taking antianginal drugs (β blockers in 22).

METHODS

All patients remained on their antianginal medication and underwent intravenous digital left ventriculography at rest and after exercise.

The digital system used was the Siemens Digitron II connected on line to a standard Siemens Angioskop angiography suite. All digital data were stored on magnetic tape for subsequent analysis. We developed suitable software in our laboratory using

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the standard Fortran compiler available for this system.

A 5 French pigtail superflow catheter was inserted percutaneously or by cut down into the antecubital vein and advanced to the right atrium. A resting digital left ventriculogram was then performed. Images were obtained in the right anterior oblique projection after injection of 40 ml non-ionic contrast medium at a flow rate of 17–20 ml/s, after a delay of 5 s to allow for pulmonary transit. We used pulsed radiation at a frame rate of 12·5 frames/s and an image matrix size of 256 × 256. All digital angiograms were performed in held inspiration to minimise motion artefact.

Immediately after the resting study, patients undertook a supine bicycle exercise test. This was in three stages of two minutes, with 12 lead electrocardiographic monitoring throughout. Exercise was terminated by angina, significant ST segment depression, fatigue, or by the end of the exercise protocol.

A second digital left ventriculogram was performed 10 s after peak exercise, as described above, in the same right anterior oblique projection.

Processing

We used mask-mode image subtraction to determine the sequence of image frames with optimal contrast opacification; from this we selected 3–5 cardiac cycles that started and ended with an end diastolic frame. We corrected the raw images for a changing background, which was principally caused by *x* ray scatter (see discussion). We used software developed in our laboratory to process the selected digital image sequences to produce phase and amplitude images by a method previously described.[5]

Image assessment

Phase and amplitude images were assessed both subjectively and objectively. Subjective assessment was performed by an independent observer blinded to the coronary anatomy. Phase and amplitude images obtained at rest and exercise were assessed for the presence of abnormalities as determined by reduced amplitude or delayed phase in three wall segments (anterior, apical, and inferior). The two digital studies were then compared for evidence of a deterioration in wall motion after exercise.

For the objective assessment of the phase and amplitude images we used an analysis technique developed in our laboratory (fig 1). We outlined the area representing the left ventricle by hand, starting at the superior border of the aortic valve plane and extending around the apex to the inferior border of the mitral valve plane. We used the phase image to determine the start and finish of the outline because there is an abrupt change in phase at these points, the atrium and aorta being markedly out of phase with the ventricle. The outline was drawn around the amplitude image of the ventricle to avoid the effect of ventricular muscle movement, which causes the ventricular phase image to extend beyond the cavity.

Once the ventricle had been outlined it was subdivided into 25 sectors of equal angles. The set of segments defined by the outer 25% of these sectors, spanning the region most closely representing the wall motion of the anterior, apical, and inferior wall regions, was then used for automatic analysis. Specific segments were taken to represent anterior (3–10), apical (11–15), and inferior (16–23) wall motion.

Mean phase and amplitude were calculated for each of the 25 segments. These values were then plotted on a graph with the segment location from aortic valve to mitral valve on the x axis and the value of phase and amplitude on the y axis.

Because normal ventricular motion can give rise to systematic regional variations in both phase and amplitude, the data were fitted by regression lines—linear for phase and second order polynomial for amplitude—to highlight areas of abnormal phase and amplitude, and also to allow normalisation of the data so that data at rest and exercise could be compared. Once the data had been normalised in this way, a plot of the difference in phase and amplitude between the rest and exercise studies was produced. We used data for the control group to derive a normal range for change in phase and amplitude. This enabled us to analyse the data from the group with coronary artery disease to detect objectively a deterioration in left ventricular performance after exercise. An abnormality was deemed to be present if the amplitude fell below or the phase rose above the derived normal range in two or more consecutive segments or in two adjacent wall regions.

The results from the objective analysis were compared with those obtained by subjective assessment.

Cineangiograms were assessed subjectively by an independent observer. A coronary stenosis of >70% was regarded as significant, and assigned to one of the three main coronary arteries: left anterior descending, left circumflex, or right coronary arteries. The wall motion of each of three left ventricular wall segments (anterior, apical, and inferior) was subjectively assessed as normal or abnormal.

Results

CONTROL GROUP (TABLE I)

The control group consisted of eight patients with normal coronary arteries or minor coronary disease. The left ventricle was reported to be abnormal on cineangiography in three of them.

Subjective reporting of the resting phase and

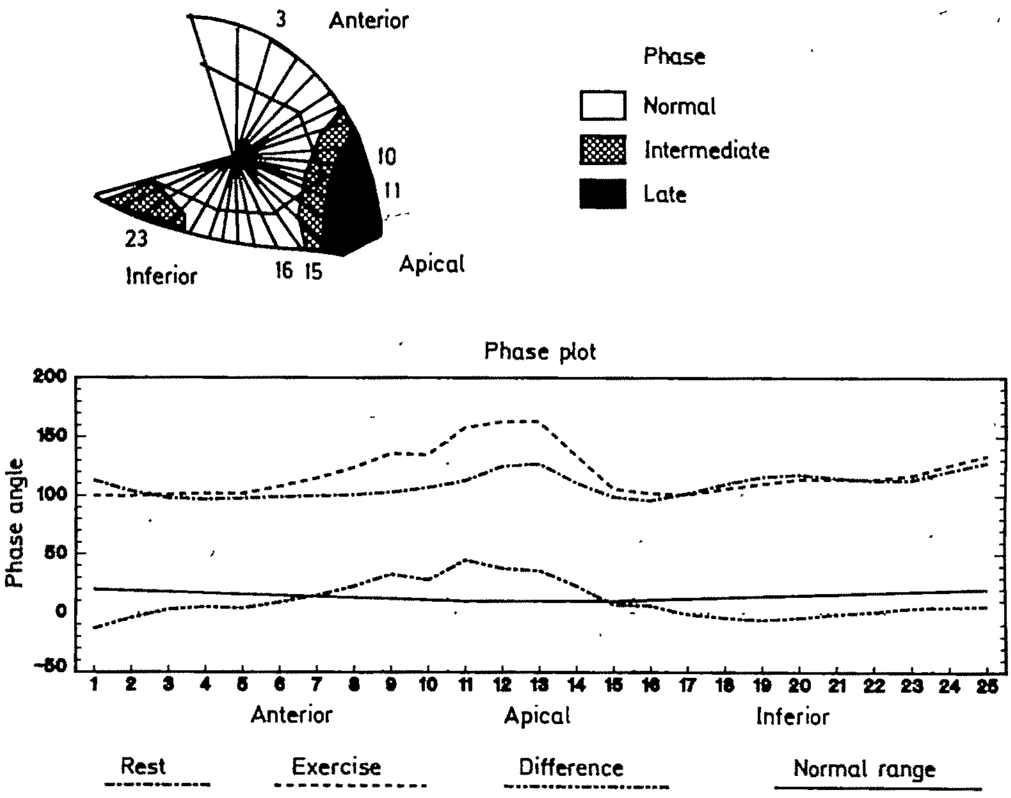

Fig 1 *An example of objective analysis method. The phase image is divided into 25 equal sectors and a plot of phase in the outer 25% produced. After normalising the data, a difference plot is derived. In this case exercise induced a new phase abnormality in the anterior and apical segments.*

amplitude images detected left ventricular wall motion abnormalities in the three patients with abnormalities on their cineventriculograms. The remaining five resting studies were reported to be normal.

All but one patient completed three stages of exercise. Two patients, one with normal coronaries, showed significant ST depression on the electrocardiogram at the end of the protocol. The mean heart rate achieved was 116 beats per minute.

After exercise in these eight patients the phase and amplitude images showed no deterioration in left ventricular function. In two of the three patients with an abnormal left ventricle at rest there was apparent improvement in left ventricular wall motion in the abnormal segments.

Table 1 *Control group*

No	*LV*	*CAD*	*Stage**	*HR†*	*P*	*E*	*Digital rest*	*Study exercise‡*	*Exercise abnormality§*	
									Subjective	*Objective*
1	An, Ap	0	III	95	–	–	An, Ap	An	–	–
2	N	0	III	125	–	–	N	N	–	–
3	N	0	III	130	–	–	N	N	–	–
4	N	0	III	130	–	+	N	N	–	–
5	Ap	0	III	125	–	–	In	N	–	–
6	An	1	III	110	+	–	Ap	Ap	–	–
7	N	2	III	110	–	+	N	N	–	–
8	N	3	II	105	+	–	N	N	–	–

See footnote to table 2 for abbreviations.
1, 2, 3, minor disease in one, two, or three vessels.

We derived a normal range for the objective analysis from this group.

CORONARY ARTERY DISEASE GROUP (TABLE 2)

Forty patients had significant coronary artery disease, 15 with one vessel disease (cases 1–15), 17 with two vessel disease (cases 16–32), and eight with three vessel disease (cases 33–40). Left ventricular abnormalities were reported on cineventriculography in 30.

The phase and amplitude images of the resting digital left ventriculograms were reported to be abnormal in 37 patients. But phase and amplitude images were normal despite abnormalities on cineventriculography in three cases, and they detected abnormalities in 10 patients with normal cineventriculograms.

Thirty one patients completed three stages of exercise and nine patients stopped at an earlier stage because of angina. The main heart rate achieved was 104 beats/min. Twenty six patients developed angina and 23 developed significant (1 mm) ST depression on the electrocardiogram. There was ST depression in six patients with one vessel disease, 10 with two vessel disease, and seven with three vessel disease.

SUBJECTIVE ANALYSIS

After exercise a deterioration in wall motion was

Table 2 *Patients with coronary artery disease (grouped according to coronary anatomy and result of exercise study)*

									Exercise abnormality§	
No	*LV*	*CAD*	*Stage**	*HR†*	*P*	*E*	*Digital rest*	*Study exercise‡*	*Subjective*	*Objective*
1	An, Ap	Ad	III	100	+	–	An, Ap	An, Ap	–	–
2	In	R	III	95	+	+	In, Ap	In, Ap	–	–
3	In, Ap	R	III	105	–	–	N	N	–	–
4	N	Cx	III	100	+	–	An, Ap	An, Ap	–	–
5	An, Ap	Ad	III	120	–	–	An, Ap	An, Ap	–	In, Ap
6	An, Ap	Ad	III	85	+	–	An	An	An	–
7	An	Ad	II	80	+	–	In	In, Ap	In, Ap	–
8	N	Cx	III	140	–	–	In, Ap	In, Ap	Ap	–
9	In	Cx	III	95	–	–	In, Ap	In, Ap	In, Ap	–
10	N	Ad	III	80	+	+	An, Ap	An, Ap	An, Ap	An, Ap
11	Ap	Ad	III	105	–	–	An, Ap	An, Ap	An, Ap	Ap
12	An, Ap	Ad	III	150	+	+	An, Ap	An, Ap	An, Ap	3
13	An, Ap	Ad	III	100	+	+	Ap	Ap	Ap	An, Ap
14	An	Ad	III	95	+	+	An, Ap	An, Ap	An, Ap	Ap
15	An, Ap	Ad	II	110	+	+	An	An	An	An, Ap
16	N	Ad, Cx	III	85	+	–	In, Ap	In, Ap	–	–
17	N	R, Cx	III	95	+	–	In, Ap	In, Ap	–	–
18	3	Ad, R	III	100	–	–	An	An	–	In
19	Ap	Ad, R	III	150	–	–	N	N	–	An
20	In	R, Cx	III	100	–	–	N	N	–	In
21	N	Ad, Cx	III	90	+	+	Ap	In, Ap	In	–
22	In	Ad, R	II	120	+	+	In, Ap	3	3	In, Ap
23	3	Ad, R	II	110	+	+	An, Ap	An, Ap	Ap	An, Ap
24	In	Ad, R	III	85	+	–	An	An, In	In	An
25	N	Ad, R	III	90	–	+	Ap	Ap	Ap	In, Ap
26	N	Ad, R	II	105	+	+	Ap	An, Ap	An, Ap	An, Ap
27	N	Ad, Cx	III	105	+	+	In, Ap	In, Ap	In, Ap	In, Ap
28	An, Ap	Ad, Cx	III	130	–	–	Ap	Ap	Ap	3
29	An, Ap	Ad, Cx	I	100	+	+	An, Ap	An, Ap	An, Ap	In, Ap
30	In	R, Cx	II	80	+	+	Ap	In, Ap	In	In
31	In	R, Cx	III	115	+	+	In	In, Ap	In, Ap	In
32	3	R, Cx	III	95	–	+	An	An, Ap	Ap	In, Ap
33	N	3	III	80	–	+	3	3	In	–
34	In	3	II	130	+	+	In, Ap	3	3	An, Ap
35	Ap	3	III	90	+	+	Ap	An, Ap	An, Ap	An, Ap
36	In, Ap	3	III	135	–	+	In, Ap	In, Ap	Ap	3
37	In, Ap	3	I	90	+	+	In, Ap	In, Ap	Ap	Ap
38	3	3	III	140	–	–	An, Ap	An, Ap	An, Ap	3
39	3	3	III	110	+	+	In, Ap	In, Ap	Ap	In, Ap
40	Ap	3	III	70	+	+	Ap	In, Ap	In, Ap	In, Ap

LV, Left ventricle from cineventriculogram; CAD, coronary artery disease; P, presence (+) or absence (–) of chest pain during exercise, E, presence (+) or absence (–) of significant ST depression during exercise; N, normal left ventricle, An, abnormality of anterior segment, Ap, abnormality of apical segment; In, abnormality of inferior segment.

3, three abnormal segments or three vessel disease; Ad, stenosis of left anterior descending artery; R, stenosis of right coronary artery, Cx, stenosis of left circumflex artery.

*Stage of exercise reached. †HR, heart rate achieved during exercise. ‡Results of phase and amplitude digital study of the left ventricle at rest and during exercise. §Segment with either deterioration or new abnormality after exercise.

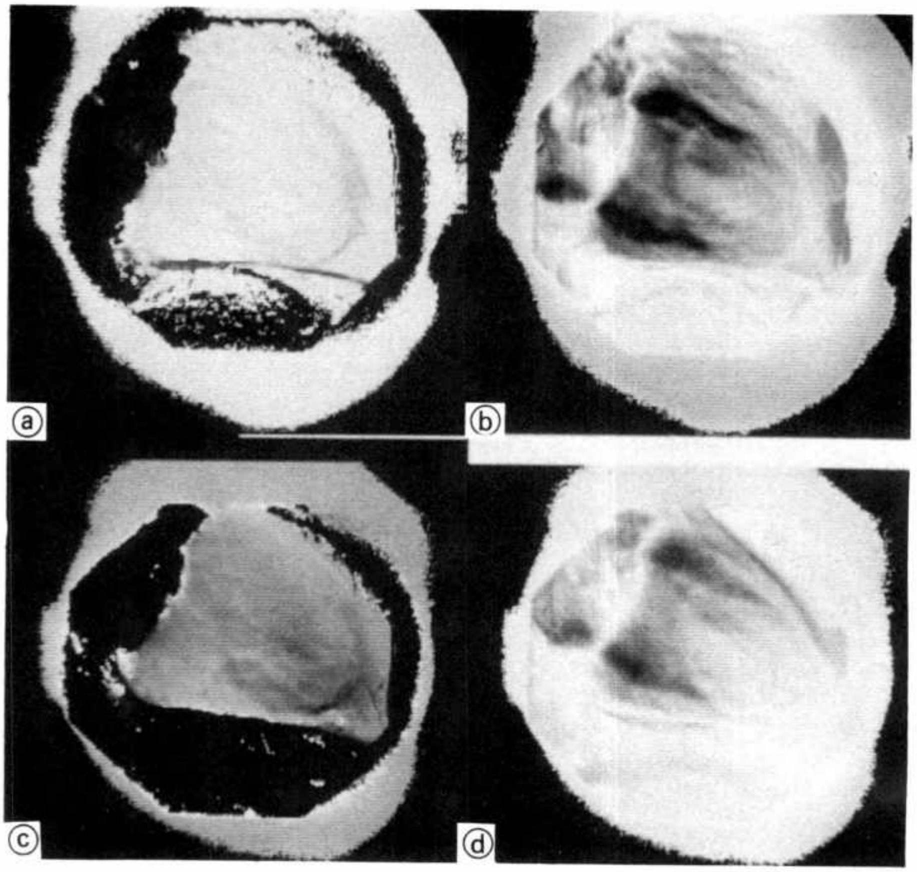

Fig 2 *The resting digital study (phase (a) and amplitude (b)) in patient 28 showed a reduction of apical amplitude. After exercise, a new abnormality of apical phase was seen (c) with a further pronounced reduction of apical amplitude (d).*

detected by subjective analysis in 30 patients. This group included all eight patients with three vessel disease (cases 33–40), 10 of the 15 patients with one vessel disease (cases 6–15), and 12 of the 17 patients with two vessel disease (cases 21–32). In 10 patients there was no change in wall motion: five patients had one vessel disease (cases 1–5) and five had two vessel disease (cases 16–20).

In all but one of the 10 patients with one vessel disease who showed a deterioration in wall motion, deterioration was confined to a segment that was abnormal at rest. In the remaining patient with an abnormality of the inferior wall at rest, there was deterioration in this segment and a new abnormality in the adjacent apical segment.

In contrast, an abnormality of a previously normal segment was detected in seven of the 12 patients with two vessel disease in whom there was a deterioration in wall motion. In all cases this new abnormality was compatible with the underlying coronary disease.

Of the eight patients with three vessel disease, six had an abnormality of two or more segments at rest. In three cases an abnormality developed in a previously normal segment and in five, previously abnormal segments deteriorated.

In the 10 patients in whom no deterioration was detected after exercise, abnormalities of wall motion were detected at rest in seven and these persisted after exercise.

OBJECTIVE ANALYSIS

When the rest and exercise studies were compared by objective means, a deterioration in wall motion was detected in seven patients with one vessel disease, 14 with two vessel disease, and seven of the eight patients with three vessel disease. In the group with one vessel disease this method did not detect four patients found to be abnormal by subjective analysis

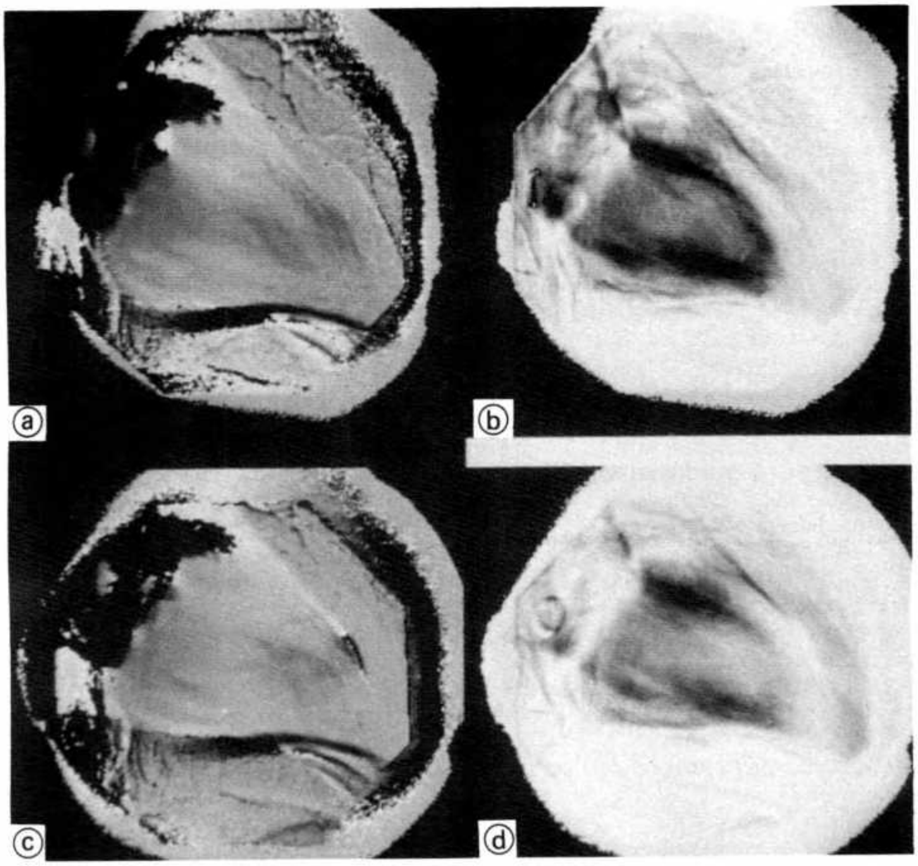

Fig 3 *The resting digital study (phase (a) and amplitude (b)) in patient 35 showed a reduction of apical amplitude. After exercise a pronounced reduction in anterior and apical amplitude was seen (d) associated with a phase abnormality in the same segments (c).*

and detected one further patient. In the group with two vessel disease the objective method missed one patient found to be abnormal subjectively, but detected three further patients. This method failed to detect one patient with three vessel disease.

Discussion

There is now evidence from recent trials that coronary surgery can improve the prognosis in certain groups of patients with ischaemic heart disease. Those with most to gain have moderate symptoms and three vessel coronary disease.[8 9] There is, therefore, much emphasis on non-invasive methods to detect the population that should proceed to the more invasive technique of coronary angiography.

Both exercise testing and nuclear thallium scanning are often used for this purpose. Both are limited, however, by false positive and false negative results.[10] Nuclear, gated blood pool scanning of the left ventricle comes closer to the requirements for the ideal test. It is also limited, however, by low spatial resolution, and the fact that, because it is an equilibrium study, images can only be acquired in the left oblique projection to avoid counts from the overlying right ventricle. First pass techniques with multicrystal cameras and short half life isotopes may overcome this latter problem, but such equipment is not readily available in most centres.

Intravenous digital subtraction left ventriculography has been used to detect exercise induced wall motion abnormalities in the same way as gated blood pool scanning. This is a first pass technique and can therefore be performed in the standard right anterior oblique projection, and also has the advantage of high spatial resolution. The technique compared well with nuclear studies, but was limited considerably by the increased subtraction artefact introduced by motion. For this reason, images must be acquired after peak exercise, but even then subjective interpretation of the images is impaired by subtraction artefact.[11]

For this reason we decided to apply the technique of phase and amplitude analysis to intravenous digital left ventriculography. This has been widely used in nuclear cardiology and allows an objective assessment of left ventricular function. Furthermore, because the analysis is based on data derived from several cardiac cycles and is not dependent on image subtraction, the artefact introduced by minor degrees of cardiac motion is minimised.

PHASE AND AMPLITUDE ANALYSIS

Phase and amplitude processing replaces the time-density variation at each image pixel by a sinusoid of best fit (calculated by standard mathematical techniques).[12] The sinusoidal variation is described completely by two parameters: its amplitude or degree of cyclic density change and its phase or relative timing of these changes. Thus the dynamic image sequence is summarised by two parametric images—variations in grey scale intensity represent local changes of the relative timing and relative magnitude of opacified dimension changes and phase changes are described in terms of fractions of a cycle, measured on a scale of 0° to 360°.

A normal ventricular phase image shows the region of the ventricular outline as a relatively constant low phase angle (light), which is sharply distinct from the atria which have a constant but different phase (darker, by about 180°). The corresponding amplitude image shows large values (dark) in regions of maximum motion inside the ventricular boundaries and shows localised variations caused for example by the inclusion of papillary muscle or by regional gradations.

Because there is little change in dimension or density in regions outside the heart they show very low amplitude and random phase. Organs such as the lung and diaphragm, which may overlie the heart and move with respiratory cycle, create severe artefact on normal digital subtraction angiography but have much reduced effects on phase and amplitude images.

The phase image of abnormal ventricles will be affected by any change in the pattern of myocardial contraction. Myocardial ischaemia induces a delay in the timing of contraction of the abnormal wall segment and this therefore produces a shift towards higher values of phase. This appears as a dark region of the ventricle on the phase image. Nuclear studies have shown that the degree of phase delay is related to the severity of the abnormality.[13]

Abnormalities of wall motion can also be detected by the demonstration of reduced amplitude, because ischaemia affects not only the timing of contraction but also the degree of fractional shortening of the affected segment. This appears as a light region of the ventricle on the amplitude image.

Since this analysis fits only the first harmonic it has enhanced sensitivity to changes occurring at the cardiac frequency but is relatively insensitive to finer details of the motion. The phase angle will be affected by any change in the pattern of myocardial contraction, and changes in timing can be detected that are quite small compared with the actual framing rate. Thus a delay in the timing of the onset of contraction, peak contraction, or relaxation of part of the myocardium will all lead to an increase in phase angle of the affected wall segment. In theory, a delay in contraction associated with early relaxation could, however, lead to no change in phase angle.

In the normal ventricle the timing of contraction of each wall segment occurs within a narrow window, and thus the normal ventricle will show a fairly uniform phase. We found this in our control group. In this group, however, we noticed a tendency for phase either to increase or decrease progressively from aortic valve to apex to mitral valve. We believe this may be related to sideways movement of the ventricle throughout the cardiac cycle, and may possibly explain the wide confidence intervals for phase found in nuclear studies.[13]

CHANGING BACKGROUND

When phase and amplitude analysis are applied to raw digital angiographic data, the resultant images are distorted. Static image regions have a significant amplitude; and a ring of zero amplitude appears inside the left ventricular boundary, which contains signals of generally lower amplitude. This results from a modulated background, which is principally the result of *x* ray scatter.

At the *x* ray energies used during digital angiography *x* ray scatter makes a larger contribution to *x* ray attenuation than *x* ray absorption. This effect can be seen around the edges of the image where the image density outside the coned field appears to be less than expected. Because the degree of scatter is proportional to the density of the structure under investigation, there will be a greater amount of scatter at end diastole when there is more contrast medium in the left ventricle than at end systole. Thus the *x* ray scatter will vary with the cardiac cycle, producing a variation in image density that has its own amplitude and is out of phase with the left ventricle. It is important to correct for this variation in *x* ray scatter when phase and amplitude images of the left ventricle are produced. Because scatter is isotropic, we have assumed this effect to be uniform throughout the image. An area of the image, distant from the left ventricle, was therefore selected and the phase and amplitude of the x ray scatter was calculated. Each image was then corrected for scatter by subtracting the calculated amplitude of scatter from the raw image data.

ANALYSIS METHODS

We used subjective and objective methods to analyse the phase and amplitude images. The character of the phase and amplitude images is such that there are advantages in both visual and quantitative analysis. On one hand the images can have a complex structure, representing complex details of anatomical motion, best assessed by expert clinical judgement that cannot yet be reproduced by automatic methods. Against this, the eye is not a reliable means of assessing relatively precise numerical information presented visually; and with automatic methods interobserver variations and the need for wide observer experience are removed. Ideally, in practice the two methods would be used to complement each other. We compared the methods because we are still seeking to validate the techniques.

The subjective interpretation was performed by one person with considerable experience in interpretation of nuclear phase and amplitude images. This method enables direct comparison of the rest and exercise images, making no assumption about left ventricular geometry, and taking into account the appearance of the entire left ventricular images. On the other hand, objective methods, although simple to perform, offer greater precision over a very much narrower analytical domain. The present method is a relatively uncomplicated process. It relies on strict geometric definition of the regions analysed, so that anatomical localisation of abnormalities may be in error—and only the outer section of the ventricle, where most significant abnormalities appear, is used. Despite these problems there is a generally good agreement between the two analysis techniques, and we believe that further refinement of the objective method would produce even closer agreement. For these reasons we attached more importance to the subjective reporting.

PATIENT DATA

The reference standard for the normal left ventricle is healthy people shown at angiography to have normal coronary arteries. Because we used invasive techniques we could only study patients with chest pain and suspected coronary artery disease who were shown angiographically to have normal or insignificantly stenosed coronary arteries. Our control group consisted of eight people, five who had normal coronary arteries and three who had only minor coronary disease. Three of these had abnormalities of the left ventricle at rest. These cannot, therefore, be regarded as healthy controls but it is in just this population that a reliable non-invasive test would avoid the need for coronary angiography. We therefore believe this to be a valid control group for this study.

The mean heart rate achieved during the supine bicycle exercise was rather low in comparison with conventional exercise testing. Supine exercise, however, is known to be associated with a lower heart rate than upright exercise.[14] Furthermore, 22 of the patients with coronary artery disease were receiving β blocking drugs. The fact that 26 of the 40 patients with coronary disease developed angina, 23 showed significant ST depression, and 30 developed new wall motion abnormalities despite relatively low heart rates suggests that the exercise was sufficiently severe.

We found phase and amplitude analysis of digital left ventriculograms to be a very satisfactory method of assessing left ventricular function both at rest and immediately after exercise. The images produced were simple to interpret subjectively, with a little experience, and this assessment of phase and amplitude agreed quite well with that obtained by a simple method of objective analysis.

This technique detected some wall motion abnormality at rest in three of the controls and 37 of the group with coronary artery disease. In 10 cases the resting digital study detected abnormalities not reported on the cineangiograms, whereas it failed to detect abnormalities seen on the cineventriculogram in three. Apical abnormalities were detected far more frequently than anterior or inferior ones, and the apex was the abnormal segment in nine of the 17 people (controls and patients) with only one abnormal segment. It is possible, therefore, that the technique of phase and amplitude analysis is overdiagnosing abnormality of the apical segment. After exercise, however, apical abnormalities were detected in 34 people, of whom 24 had shown a deterioration compared with resting function. If this analysis is overdiagnosing apical abnormalitiies, it seems unlikely that this effect would be emphasised in the exercise studies. It therefore seems more likely that the rest images were detecting minor apical abnormalities that became more apparent during ischaemia. It also seems from our data that the ventricular apex is the wall segment most vulnerable to myocardial ischaemia, regardless of the distribution of coronary stenoses.

The next question we must answer is whether this technique can detect the patients with multivessel disease who need further investigation, and whether it is possible to select out the patients with minor and single vessel disease who need only relief of symptoms. The standard technique at present for studying exercise induced myocardial ischaemia is exercise stress testing, and in particular the development of exercise induced ST segment depression on the electrocardiogram. In this study 25 people (controls and patients) developed significant ST depression and this group included 17 of the 25 patients with multivessel disease. One patient with three vessel disease was missed, however, and two patients with either normal coronary arteries or minor disease were falsely identified. We therefore looked to see whether our digital technique was more selective.

Any technique that relies on the localisation of myocardial ischaemia to predict the underlying coronary anatomy is limited. In the first place it is necessary for ischaemia to occur. A patient can have severe coronary artery disease and not show myocardial ischaemia on exercise, and such patients cannot be detected. Secondly, when ischaemia does occur, even in the presence of multivessel disease, exercise will be limited by symptoms resulting from the area of myocardium that becomes ischaemic first. Therefore the wall motion abnormality that is shown may be confined to one wall segment. Furthermore, a stenosis of a single coronary artery may produce abnormalities in two adjacent segments (anterior and apical) or (inferior and apical) if the artery is large enough. Thus the number of abnormal segments alone cannot determine the coronary anatomy.

In our control group, no patient developed a deterioration in left ventricular function on exercise. Two of the three patients with an abnormal ventricle at rest showed an improvement with exercise.

Subjective analysis showed no deterioration in wall motion on exercise in five of the patients with one vessel disease. Of the remaining 10 patients, exercise induced deterioration in wall motion was confined to previously abnormal segments in nine, and in the last case an inferior abnormality extended to the apex. Thus in this group, exercise was rarely associated with extension of the ischaemic area, and in all cases the abnormality was consistent with a single coronary lesion.

In the group with two vessel disease, however, a previously normal segment was more often affected (seven cases). In five cases our technique failed to detect exercise induced abnormalities, and these patients could not therefore be distinguished from the group with one vessel disease. In the remaining five patients a deterioration was detected that affected previously abnormal segments, including the apical segment in all five.

A deterioration in wall motion after exercise was detected in all eight of the patients with three vessel disease. New abnormalities were detected in three. This group contained only two patients with a single abnormal wall segment at rest, and after exercise all patients had two or three abnormal segments.

Thus this method detected 20 of the 25 patients with multivessel disease, and none with normal coronary arteries or minor disease. It did, however, identify more patients with significant one vessel disease than the electrocardiographic changes alone.

Neither digital left ventriculography nor ST segment analysis was totally specific for multivessel coronary disease. We believe that our technique may help when the results of exercise testing are misleading and in particular in the management of patients with a false positive exercise test. Furthermore, the combination of ST depression and an exercise induced abnormality in wall motion is more specific for multivessel disease than either marker alone, although some sensitivity is lost.

We have developed a new method of detection of exercise induced myocardial ischaemia, namely phase and amplitude analysis of exercise intravenous digital left ventriculograms. This technique detected left ventricular wall motion abnormalities both at rest and after exercise and provided some insight into the underlying coronary artery disease. In our series we subjectively identified all the patients with three vessel disease, and in general the extent of the induced ischaemia was dependent on the number of coronary stenoses. Phase and amplitude analysis of exercise digital left ventriculograms may therefore help in the selection of those patients for whom further investigation by coronary angiography is indicated.

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The variable effects of angiotensin converting enzyme inhibition on myocardial ischaemia in chronic stable angina

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SUMMARY The effect of angiotensin converting enzyme inhibition on myocardial ischaemia was studied in 12 normotensive patients with chronic stable angina and exercise induced ST segment depression. The study was randomised, double blind, placebo controlled, and crossover with treatment periods of two weeks. Enalapril was used to inhibit angiotensin converting enzyme. Assessment was by angina diaries and maximum symptom limited treadmill exercise tests. The results for the whole group showed a significant reduction in systolic blood pressure at rest and at peak exercise. Mean total exercise duration was 466 s (95% confidence interval 406 to 525) when the patients were taking placebo and 509 s (436 to 583) when they were taking enalapril. Four patients prolonged their total exercise time (mean 450 to mean 591 s) by more than 20%. Two patients, however, developed ischaemia earlier on exercise and reduced their total exercise duration (mean 490 to mean 390 s).

Although angiotensin converting enzyme inhibition tended to reduce myocardial ischaemia in the group as a whole, some patients improved while others deteriorated. Thus the effects of enalapril are variable and this may have important implications when enalapril is used to treat heart failure in patients with underlying severe ischaemic heart disease.

Angiotensin converting enzyme inhibition reduces left ventricular diastolic pressure, aortic systolic pressure, and sympathetic drive.[1-3] Such effects should reduce myocardial work and oxygen consumption and hence may be beneficial to patients with angina. Angiotensin converting enzyme inhibitors are used successfully to treat coexisting hypertension and heart failure in patients with coronary artery disease although their actual effect on myocardial ischaemia is not defined.

We tested the hypothesis that angiotensin converting enzyme inhibition reduces myocardial ischaemia in patients with chronic stable angina.

Patients and methods

Twelve patients (11 men and one woman; mean age 55 years (range 46–70 years)) with chronic stable angina that had not increased in frequency or duration in the preceding three months were entered into the trial. The frequency of their angina varied from one attack per month to five attacks per day. All patients were normotensive, had a positive exercise test with >0·1 mV linear or downsloping ST segment depression, normal electrolytes, and normal renal function. Three patients had sustained a previous myocardial infarction and two other patients had undergone coronary artery bypass grafting ten years before.

The protocol was approved by the National Heart and Chest Hospitals ethics committee and written informed consent for the trial was obtained from all patients.

STUDY DESIGN

We investigated the anti-ischaemic effect of 10–20 mg of enalapril once daily in a randomised, double blind, placebo controlled, crossover study with two treatment periods of two weeks each. All drug treatment apart from glyceryl trinitrate was stopped. After a one week washout period on glyceryl trini-

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trate alone, the patients were randomised to receive either enalapril 10 mg once a day for one week increasing to 20 mg once a day for a further week, or matching placebo. After a one week washout period patients were crossed over to receive either placebo or enalapril for a further treatment period of two weeks. The dose of enalapril or matching placebo was not increased after the first week of treatment if the resting systolic blood pressure was < 100 mm Hg, if the patient was experiencing side effects, or the patient had become symptom free.

Patients were assessed by angina diaries and symptom limited treadmill exercise tests with a modified Bruce protocol[5] of three minute stages. The treadmill exercise tests were performed 1–5 hours after drug administration, at the same time of day for each patient, on the last day of each treatment period.

A 12 lead electrocardiogram was recorded before exercise, every minute during exercise, and for five minutes after stopping. Blood pressure was recorded with a cuff before exercise and at every three minutes during exercise. The patients were asked to report when their angina started and when it worsened. Exercise was stopped by disabling angina. The electrocardiograms were analysed to determine heart rate and time to 1 mV ST segment depression. Total exercise time was also recorded. Serum concentrations of enalaprilat were measured by radioimmunoassay of blood samples taken immediately after exercise testing.[6]

STATISTICAL ANALYSIS

All data were analysed without knowledge of the patients' treatment. Measurements were made of the time to onset of 0·1 mV ST segment depression and total exercise duration; and of heart rate, blood pressure, and rate-pressure product at rest, at 0·1 mV ST segment depression, and at peak exercise.

For statistical testing, a Hills and Armitage crossover analysis was performed. The differences between systolic blood pressure measurements were compared by a Student's *t* test. The results of exercise testing were analysed to determine the differences for each patient in exercise time and time to 1 mV ST segment depression between placebo and enalapril.

Results

All 12 patients completed the study. As a result of an error in randomisation, seven patients received enalapril and five patients received placebo as their first treatment. A non-orthogonal analysis of variance showed that there had been no treatment effect, period effect, or treatment period interaction. The magnitude of the treatment effect on the total exercise time was 31 s (95% confidence interval from −46 to +109 s), and on the time to 1 mV ST depression was 51 s (95% confidence interval −33 to +135 s).

During the enalapril period, three patients (numbers 2, 5, 11) did not have the dose of enalapril increased beyond 10 mg daily because systolic blood pressure was already < 100 mm Hg. No patient on placebo had a significant reduction in systolic blood pressure.

HAEMODYNAMIC CHANGES

Systolic blood pressure at rest fell from 134 (16) (1 SD) on placebo to 118 (15) mm Hg and at peak exercise from 165 (30) to 146 (27) mm Hg ($p < 0·05$) (fig 1). Similarly, the rate-pressure product at rest fell from 10 329 on placebo to 9 487 on enalapril and at peak exercise from 20 259 to 17 930 ($p < 0·05$). Heart rate at rest and peak exercise was unaffected by enalapril.

MYOCARDIAL ISCHAEMIA

For the whole group, total exercise duration increased from 466 s (95% confidence interval 406 to 525) during placebo to 509 s (436 to 583) during enalapril (fig 2). The difference between the sample mean total exercise duration on enalapril and placebo was 43 s (95% confidence interval −55 to +142 s); the *t* test statistic was 2·07 with 11 degrees of freedom. Exercise duration 0·1 mV ST segment depression rose from 345 s (95% CI 300 to 390) on placebo to 387 s (95% CI 322 to 453) during enalapril (fig 3). The difference between the sample mean exercise duration to 1 mV ST depression was 42 s (95% CI −48 to +134 s); the *t* test statistic was 2·07 with 11 degrees of freedom.

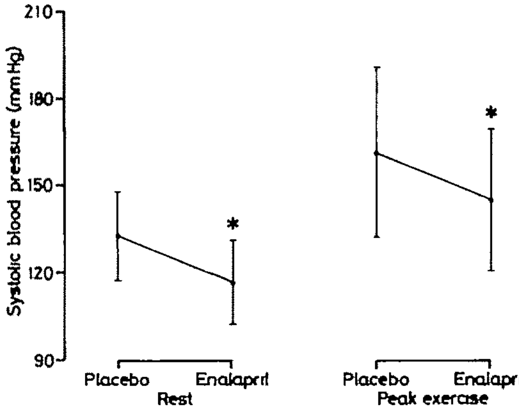

Fig 1 *Systolic blood pressure at rest and at maximum exercise on placebo and enalapril Mean (1 SD) is shown.* *$p < 0·05$.

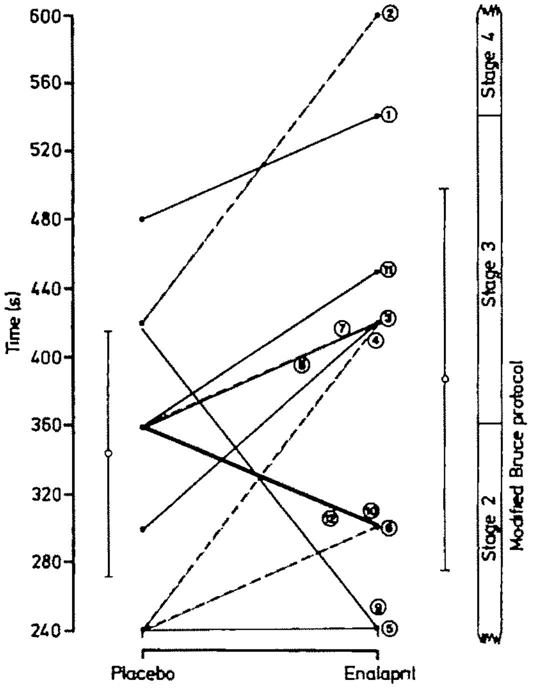

Fig 2 *Total treadmill exercise duration before and during treatment with enalapril. Dotted lines indicate the four patients with improvement of total exercise duration by more than 20%. Mean (1 SD) given for whole group. Individual patients are numbered.*

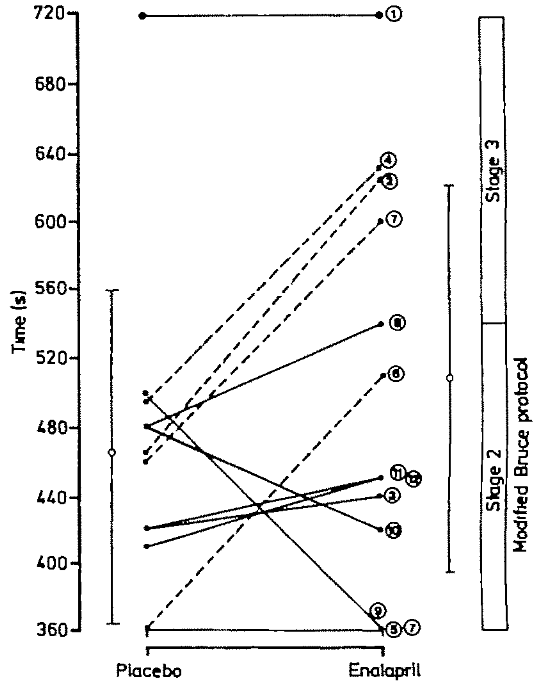

Fig 3 *Duration of treadmill exercise to 1 mV ST segment depression. Dotted lines indicate the four patients whose total exercise duration improved considerably. Mean (1 SD) given for the whole group. Individual patients are numbered.*

Four patients (numbers 2, 4, 6, and 7: shown as dotted lines in figs 2 and 3) had an increase in total exercise time of more than 20% on enalapril compared with placebo (fig 4).

Two patients (numbers 9, 10) showed reduction of both their total exercise time (fig 4) and the time to 0·1 mV ST segment depression (fig 5). One of these patients (number 9) also had considerable reduction in systolic blood pressure at rest from 150 to 110 mm Hg (mean fall for group 16 mm Hg). The fall in the peak exercise blood pressure in this patient did not differ from the group mean.

There were no clinical differences in the characteristics of our patients that determined the effect of enalapril on myocardial ischaemia.

SYMPTOMS

The frequency of angina attacks and glyceryl trinitrate consumed were not altered by enalapril. Three out of the four patients whose exercise times improved considerably, also had a reduction in the mean number of angina attacks on enalapril from 21 to 11 attacks per week and a reduction in glyceryl trinitrate consumption from 11 to nine tablets per week. The fourth patient was unaffected, having one angina attack and consuming one glyceryl trinitrate tablet per week on both placebo and enalapril. The two patients who had a deterioration in both total exercise duration and time to 1 mV ST segment depression had a rise in angina attacks on enalapril from 12·5 to 16·5 per week and glyceryl trinitrate consumption rose from 11 to 13·5 tablets per week.

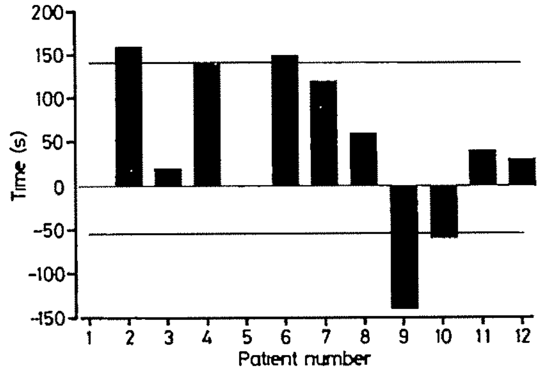

Fig 4 *Change in total exercise time during treatment with enalapril compared with placebo. The results are shown for individual patients. 95% confidence interval is shown.*

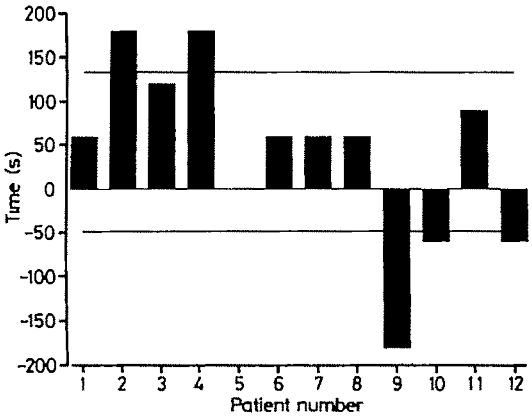

Fig 5 *Change in time to 1 mm ST segment depression during treatment with enalapril compared with placebo. The results are shown for individual patients. The 95% confidence interval is shown.*

DRUG CONCENTRATIONS

Serum concentrations of enalaprilat 2–5 hours after patients had taken enalapril ranged from 24 to 90 ng/ml (mean 56). The activity of angiotensin converting enzyme is almost completely inhibited by a concentration of 10 ng/ml.[6]

LABORATORY VALUES

Laboratory values for routine haematological and biochemical variables remained within the normal ranges for all patients during the study. Weight was unchanged during the study (enalapril 77·5 (13·8) kg, placebo 78·0 (13·5) kg).

SIDE EFFECTS

When taking enalapril two patients experienced mild disorientation that subsided spontaneously. Treatment was not interrupted.

Discussion

Enalapril is a prodrug that is hydrolysed to enalaprilat, its active metabolite.[7] This angiotensin converting enzyme inhibitor reduces plasma concentrations of angiotensin II and aldosterone and this is associated with a rise in plasma renin activity.[4] During the treatment phase of this randomised double blind study we saw a fall in blood pressure without reflex tachycardia as was seen in many other studies. Consequently, there was a fall in the rate pressure product in all of the patients. The indices of myocardial ischaemia (total exercise test and time to 1 mV ST segment depression) tended to improve in the group as a whole. Interestingly, four patients seemed to show a considerable improvement in these variables (increasing their total exercise time by more than 20%) and two patients deteriorated. There was no overall change in episodes of angina or number of glyceryl trinitrate tablets consumed during the enalapril phase as compared with placebo. This is not surprising, however, as these patients had mild symptoms and did not require much glyceryl trinitrate even during the placebo phase. Why then, did the myocardial ischaemia seem to improve in some patients and deteriorate in others taking enalapril?

There are several mechanisms by which angiotensin converting enzyme inhibition might ameliorate myocardial ischaemia. Firstly, in normotensive individuals enalapril reduces blood pressure without inducing reflex tachycardia[8] and the rate-pressure product, which is an index of myocardial oxygen demand,[9] is therefore reduced. Captopril has been shown to reduce the rate-pressure product and myocardial ischaemia when the systolic blood pressure is greater than 100 mm Hg.[10]

Second, there is evidence in animals and in man that angiotensin converting enzyme inhibition can affect coronary blood flow. In laboratory animals with normal coronary arteries, coronary vascular resistance is increased by angiotensin II[11] and the coronary vascular bed can convert angiotensin I to angiotensin II locally. Enalapril is an angiotensin antagonist in isolated coronary arteries[12] and antagonises the coronary vasoconstrictor effect on angiotensin II.[13] In one study in dogs given teprotide (an angiotensin converting enzyme inhibitor) coronary blood flow increased.[14] When it was given to a group of patients who did not have significant coronary artery disease, teprotide improved coronary artery blood flow in some patients and it was suggested that the renin angiotensin inhibition may have affected the regulation of coronary flow.[15]

Third, there is evidence in man that prostacyclin may be involved in the control of coronary artery blood flow.[16] The evidence that angiotensin converting enzyme inhibition may affect prostaglandin synthesis is only indirect. The antihypertensive effect of captopril is attenuated by indomethacin, a prostaglandin synthesis inhibitor. A similar role for enalapril has not yet been found in man.

The open trial of captopril in coronary artery disease showed significant improvement in ST segment depression during an exercise test after 48 hours' treatment.[17] Other clinical studies of angiotensin converting enzyme inhibition in ischaemic heart disease have focused on patients with additional hypertension or heart failure. In one study of eight patients with hypertension and stable angina, there was no improvement or deterioration in symptoms or global myocardial metabolism.[18] In an open study of α methyldopa versus captopril in 12 hypertensive patients with coronary artery disease, both drugs had the same antihypertensive effect, but captopril was associated with a significant improvement in ST segment depression on exercise.[19]

More recently, the active metabolite of enalapril (enalaprilat) has been used intravenously in 14 patients with heart failure, eight of whom had ischaemic heart disease.[20] In these patients there was a significant but transient reduction in myocardial oxygen extraction and an increase in coronary sinus oxygen saturation, suggesting coronary artery vasodilatation. In three of the patients with ischaemic heart disease there was also amelioration of abnormal myocardial lactate production, and it was proposed that this represented a reduction in myocardial ischaemia.

Drugs that act as vasodilators may also have the potential to make myocardial ischaemia worse.[17 21 22] The reduction in the rate-pressure product and hence myocardial oxygen demand has been significantly correlated with a reduction in coronary sinus blood flow in patients with heart failure.[23] In another study changes in coronary sinus flow paralleled changes in perfusion pressure.[24] In a study of heart failure secondary to ischaemic heart disease, captopril did not improve coronary artery blood flow and it was noted that despite improved left ventricular function and reduction in the metabolic cost, myocardial ischaemia could be precipitated in some patients.[25] Thus reduction in oxygen supply to the myocardium may outstrip reduction in oxygen demand obtained from improvement in left ventricular function and hence precipitate worse myocardial ischaemia. Such a mechanism in our patients remains speculative because the site and severity of coronary artery stenoses and the relation between the changes in perfusion pressure and coronary blood flow were not measured. In the presence of a severe fixed stenosis where there may be little coronary reserve, vasodilators may divert blood away from the ischaemic myocardium to non-ischaemic zones. Such a mechanism of coronary steal has been shown experimentally with arteriolar vasodilators[26] and in man.[17]

In conclusion, in a double blind, crossover, randomised study of enalapril versus placebo in normotensive patients with chronic stable angina, we found that enalapril tended to reduce myocardial ischaemia in the group; this may be clinically important but larger studies are needed before definitive conclusions can be drawn. Four of the 12 patients showed a considerable improvement but two became worse. From the available clinical data it is not possible to predict in advance which patients will benefit or deteriorate.

Ischaemic heart disease is often the underlying cause of heart failure. Although myocardial ischaemia may be less important in patients with chronic heart failure than in patients with normal ventricular function, the beneficial effects of angiotensin converting enzyme inhibitors in heart failure may be offset if myocardial ischaemia is made worse. These drugs should be used, therefore, with caution in heart failure caused by ischaemic heart disease.

We thank Merck, Sharp and Dohme for supplies of enalapril and placebo.

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Diabetes mellitus as a risk factor for acute myocardial infarction in Asians and Europeans

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SUMMARY Ischaemic heart disease is commoner among immigrants from the Indian subcontinent than among Europeans in the United Kingdom. The excess cannot be accounted for by differences in smoking, blood pressure, or lipid concentrations. There is, however, an increased prevalence of diabetes mellitus in the Asian population. Separate estimates of the relative risk of acute myocardial infarction associated with diabetes from parallel case-control studies were made to compare the importance of diabetes as a risk factor in the two ethnic groups. For Asians the relative risk was 3·3 (95% confidence interval 1·9 to 5·8) and for Europeans 1·3 (1·0 to 1·7). Calculations of population attributable risk indicated that clinical diabetes mellitus accounts for 21% of the incidence of myocardial infarction in Asians but only 3% of the incidence in Europeans.

Diabetes mellitus is of sufficient quantitative importance as a risk factor to account for the whole of the observed excess of deaths from ischaemic heart disease among Asians in the United Kingdom.

Ischaemic heart disease is commoner among immigrants from the Indian subcontinent (Asians) to the United Kingdom than among Europeans.[1-3] From 1970 to 1978 the standardised mortality ratio for ischaemic heart disease in Asians in England and Wales was 119 for men and 128 for women.[1] Studies in Leicestershire and east London have confirmed the increased risk of acute myocardial infarction among Asians.[4,5] The incidence of ischaemic heart disease was also reported to be disproportionately high among Asian migrants in Trinidad and elsewhere.[6]

The increased risk of ischaemic heart disease among Asians cannot be attributed to a higher prevalence of the major known risk factors, namely smoking, hypertension, and hypercholesterolaemia. Smoking is probably not commoner among Asians than Europeans,[7] with the exception of Bangladeshis.[7a] This view is corroborated by the low mortality from carcinoma of the bronchus in Asians.[2] Neither blood pressure[8] nor dietary and plasma lipids[7] seem to be higher in Asians than in Europeans.

There is, however, clear evidence from national mortality statistics,[2] from hospital activity analysis data,[4] and from surveys[9,10] of a higher prevalence of diabetes mellitus among Asians. The excess is of non-insulin dependent diabetes. It is generally accepted that clinical diabetes is a risk factor for ischaemic heart disease in the predominantly white populations in which the association has been measured,[11-14] though lesser degrees of glucose intolerance are probably not.[15] We wished to establish whether clinical diabetes is of sufficient importance as a risk factor to account for the higher incidence of myocardial infarction among Asians. To this end we performed parallel case-control analyses in these two ethnic groups in Leicester, calculating for each the relative risk of myocardial infarction in diabetic individuals compared with non-diabetic individuals. These relative risk estimates were then used to calculate the proportion of the incidence of myocardial infarction in the two groups that was attributable to clinical diabetes mellitus (population attributable risk or aetiological fraction).

Patients and methods

We studied all 50 Asian and 443 European patients with myocardial infarction aged ≥ 45 admitted to the coronary care unit, Leicester Royal Infirmary, from

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January 1987 to February 1988 inclusive. The diagnosis of myocardial infarction was based on the presence of at least two of the following criteria: a history suggestive of chest pain of cardiac type; evolving electrocardiogram changes with ST elevation; an increase in serum creatine kinase to at least twice the upper limit of the normal laboratory range. A standard patient record was completed by the admitting doctor as part of the admission procedure. It included the ascertainment of previously diagnosed diabetes mellitus and its treatment from the patient (using interpreters if necessary). Of the 51 European diabetic patients, 22% were taking insulin and 51% oral hypoglycaemic agents. For the 15 Asians with diabetes the corresponding figures were 60% and 27% respectively. No biochemcial or other results acquired during the hospital stay were used to establish the diabetic state for the purpose of this study. The doctor completing the patient record and assigning the diagnosis of myocardial infarction was not aware of the hypothesis being tested. Patients of Asian descent were identified as such in the coronary care unit database by inspection of names[4]; no attempt was made to classify subjects by place of birth.

Reference data for the prevalence of clinical diabetes in the base population from which the cases arose were obtained from a survey carried out in part of the catchment area of the hospital within the city of Leicester. The survey included about 35% of the Asian and 10% of the European adult population of the city and has been described in detail elsewhere.[9] Cases of clinical diabetes mellitus were ascertained from analysis of diabetic clinic records and specialist health visitor records. The diagnosis was made on a documented history of thirst and polyuria and a random venous plasma glucose of ⩾ 11·1 mmol/l in accordance with the World Health Organisation definition.[16] The health visitor service for diabetic patients is an important part of the community care in the city and is notified of newly diagnosed cases by hospital medical and nursing staff and general practitioners. The population denominator was extrapolated from the 1981 census data. About 90% of the Asians originated from the Gujerat region of India, having migrated via East Africa.[17]

The relative risk of myocardial infarction associated with diabetes was estimated for Asians and Europeans separately. Confidence intervals were calculated by Miettinen's test based method.[18] Stratified analysis was then performed for the age ranges 45–64 and ⩾ 65 years; we derived overall estimates of relative risk and 95% confidence intervals for each ethnic group using precision based weights.[19]

We calculated population attributable risk (AR_p) for each ethnic group using the relevant age adjusted estimate of relative risk (RR_p) and observed prevalence (P_p) of clinical diabetes in the survey sample by the following formula[20]:

$$AR_p = \frac{P_p(RR_p - 1)}{P_p(RR_p - 1) + 1} \times 100\%$$

Confidence intervals for the population attributable risk were calculated from the normal approximation[21] of the distribution of $\ln(1 - AR_p)$.

Results

The large prevalence study in the population in the catchment area gave precise estimates of the age specific prevalence of diabetes mellitus in the two ethnic groups (figure). The excess of diabetes among Asians is of the non-insulin dependent type. For the present study all diabetes was first considered in a single category. Table 1 shows the results of the case control analyses for Asians. There was a highly significant association between diabetes and myocardial infarction among Asians, with an age adjusted point estimate of relative risk of 3·3 ($p < 0·0005$). The strength of the association was similar in both age strata, indicating lack of interaction between age and diabetes as determinants of risk.

Table 2 shows the results for the European study group. The age adjusted relative risk estimate of 1·3 was of borderline statistical significance at the 5% level. Relative risk was constant across the age ranges, as in the Asian group.

Table 3 shows the analysis by treatment (dichotomised into insulin-treated and treated by oral hypoglycaemic agents or diet or both) for each ethnic group. Among the Asians there is a strikingly high relative risk for insulin treatment of 9·9 ($p < 0·0005$) compared with a non-significant relative risk estimate for treatment with oral hypoglycaemic agents or diet. This observation should be interpreted cautiously because of the small numbers in the analysis and more data are needed to confirm it.

Calculations of population attributable risk from the overall estimates of relative risk and the observed

Table 1 *Case-control analyses for Asians*

Asians	*Cases*	*Controls*	*Relative risk (95% CI)*
Unstratified analysis:			
Non-diabetic	35	6143	
Diabetic	15	806	3·3 (1·8–5·9)
Stratum 45–64 years:			
Non-diabetic	24	4308	
Diabetic	10	527	3·4 (1·7–6·8)
Stratum 65+ years:			
Non-diabetic	11	1835	
Diabetic	5	279	3·0 (1·1–8·3)

Adjusted risk ratio over age strata (variance weighted) 3·3 (1·9–5·8).

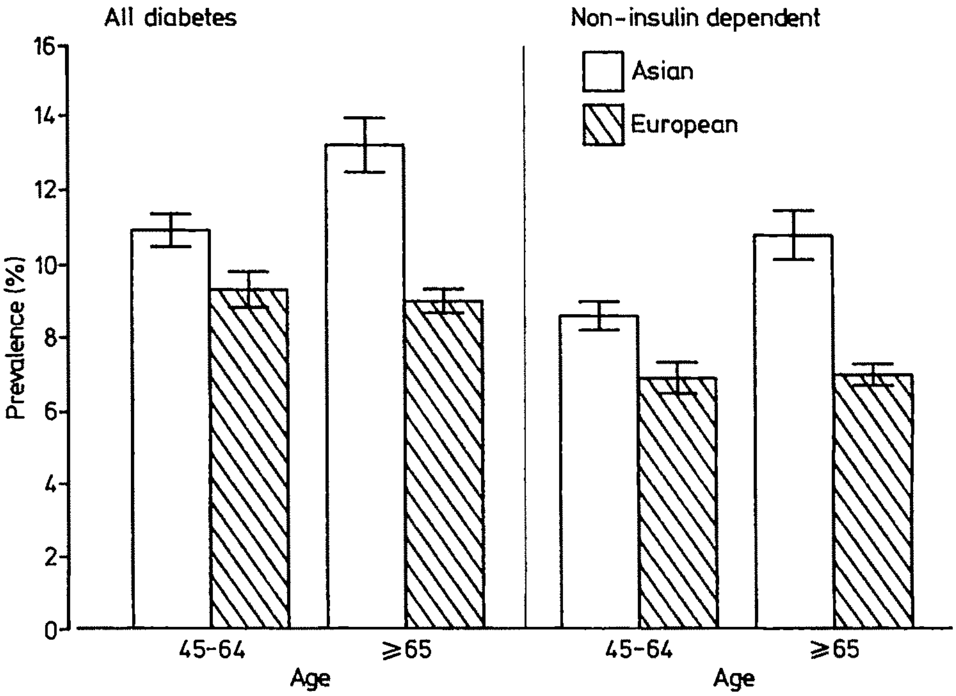

Figure *Mean (SE) age-specific prevalence of known diabetes and of known non-insulin dependent diabetes in Asians and Europeans in Leicester.*

prevalence of diabetes in the community indicate that 21% (95% confidence interval 5 to 34%) of the incidence of acute myocardial infarction in Asians is attributable to clinical diabetes mellitus. For Europeans, the population attributable risk was 3% (0 to 6%). When we used the simplest model (in which standardised ischaemic heart disease mortality is equal in Asians and Europeans in the absence of the factor of diabetes and is then scaled up by 100/79 in Asians and 100/97 in Europeans to allow for the differential effect of this risk factor) the predicted mortality from ischaemic heart disease in Asians was 123% of that in Europeans. This accords well with the observed standardised mortality ratios of 119 for Asian men and 128 for Asian women.[1] This assumes that (*a*) the combined effect of all coronary risk factors other than clinical diabetes is equal in the two ethnic groups, (*b*) that there is a similar multiplicative interaction of diabetes with other risk factors in both groups, and (*c*) that the case fatality rate is also equal. The validity of these assumptions is currently being tested in further studies.

Table 2 *Case-control analyses for European patients*

Europeans	*Cases*	*Controls*	*Relative risk (95% CI)*
Unstratified analysis:			
Non-diabetic	392	9923	
Diabetic	51	993	1·3 (1·0–1·8)
Stratum 45–64 years:			
Non-diabetic	138	3189	
Diabetic	19	327	1·3 (0·8–2·2)
Stratum 65+ years:			
Non-diabetic	254	6734	
Diabetic	32	666	1·3 (0·9–3·3)

Adjusted risk ratio over age strata (variance weighted) 1·3 (1·0–1·7).

Table 3 *Analysis by treatment for both ethnic groups*

	Cases	*Controls*	*Relative risk (95% CI)*
Asian:			
Non-diabetic	35	6143	
Insulin	9	160	9·9 (5·4–18·2)
Oral agents/diet	6	646	1·6 (0·7–3·9)
European			
Non-diabetic	392	9923	
Insulin	11	236	1·2 (0·7–2·1)
Oral agents/diet	40	757	1·3 (0·9–1·8)

Discussion

In the present study we made no estimate of relative risk of myocardial infarction in Asians and Europeans and its design does not permit such a calculation. The evidence that ischaemic heart disease is commoner among Asians than among Europeans in the United Kingdom is consistent from several sources, most notably national mortality statistics. Our objective was to measure the importance of diabetes mellitus as a coronary risk factor both for the individual (relative risk) and for the community (population attributable risk) within each ethnic group. The results show that clinical diabetes is more important by either criterion in Asians than in Europeans and is a risk factor of sufficient magnitude to account for the excess of deaths from ischaemic heart disease among Asians.

Many prospective studies of diabetes mellitus in relation to myocardial infarction have used some direct measure of glycaemia (with or without an oral glucose load) to establish the diabetic state.[12 14 22-24] Such an approach cannot validly be used in case-control studies because of the disturbance of metabolic control in the patients at the time of infarction. If tests are delayed until the recovery phase they can only be applied to survivors, who will be unrepresentative of all incident cases if early prognosis differs in patients with diabetes and those without, as has been reported.[25] Case-control studies have distinct advantages of efficiency and statistical power over cohort studies and in order to use this study design we defined history of clinical diabetes as the factor of interest rather than any biochemical measure. This definition, which was also used in the Tecumseh cohort study,[26] has the advantage of being categorical and obviates the need to divide continuous measures of glycaemia arbitrarily into ranges of normal, impaired glucose tolerance, and diabetic. In addition, a large body of prospective data has failed to provide convincing evidence that asymptomatic hyperglycaemia is a risk factor for ischaemic heart disease.[15]

Leicester Royal Infirmary provides coronary care facilities for the whole of the city and surrounding county without any differential referral patterns for patients with diabetes. The reference data came from a substantial sample of the base population providing the cases, rather than from "controls" chosen for the study. Selection bias was thereby avoided and statistical power maximised for the available number of cases. A potential disadvantage is the possibility of information bias since the diabetic state was not ascertained in exactly the same way in the cases and the controls. However, the methods were identical for both Asians and Europeans and any bias would be likely to operate equally in the two groups without invalidating the comparison between them. In addition, the finding of an increased relative risk in the Asians with diabetes is most striking in the insulin treated group, in whom diabetes is least likely to be incorrectly ascertained either for the cases or the controls.

It is unlikely that insulin treatment itself increases the risk of myocardial infarction among Asians with diabetes. Insulin dependent (type I) diabetes seems to be no more common among Asians than among Europeans, certainly during childhood.[27] It is more plausible that insulin treatment among adult Asians identifies a group of individuals with type II diabetes who have failed to be controlled by diet and oral hypoglycaemic agents.

The mechanism of the association between diabetes mellitus and acute myocardial infarction is not yet clear.[28] A recent study of coronary risk factors in east London found that Bangladeshis had a threefold greater prevalence of diabetes than Europeans.[7a] In addition, Bangladeshis without a history of diabetes showed a twofold greater serum insulin response to an oral glucose load than Europeans. In the light of these data a unifying hypothesis was proposed whereby relative insulin resistance among Asians leads to hyperinsulinaemia and consequent lipoprotein abnormalities favouring the development of coronary atherosclerosis. It is important to recognise, however, that acute myocardial infarction represents the summation of two processes: the gradual development of coronary atherosclerosis and a subsequent rapid occlusion which is nearly always thrombotic.[29] The link between diabetes and myocardial infarction might operate through either or both of these to produce the association observed here.

Under certain circumstances the relative risk associated with a particular factor can be influenced by the prevalence and strength of other risk factors in the population studied.[30] Further study of the known coronary risk factors in Asians is needed both to clarify the link between diabetes and myocardial infarction and to assist the planning of primary prevention. Mortality from ischaemic heart disease in the United Kingdom is now among the highest is the world and calls for an ambitious policy to control risk factors as has been successfully applied in Finland.[31] The present study indicates that primary prevention among Asians should be particularly directed towards those with diabetes.

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Diastolic function after cardiac and heart-lung transplantation

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SUMMARY The mechanical efficiency of left ventricular contraction and relaxation, the asynchrony of the onset of left ventricular relaxation, the time constant of left ventricular isovolumic pressure decay, and left ventricular chamber and myocardial stiffness were analysed in 32 patients after cardiac (24) and heart-lung transplantation (8). After cardiac transplantation left ventricular myocardial stiffness was increased and a mild degree of incoordinate contraction and relaxation was seen. In contrast, after heart-lung transplantation diastolic function was almost normal. Impairment of passive diastolic properties was significantly related to the ischaemic time of the donor heart and the donor's age. The index of left ventricular asynchrony was related to the ischaemic time and the recipient's age. The interval between transplantation and study did not influence the number of rejection episodes.

This study confirms the presence of diastolic dysfunction after cardiac transplantation. Impairment of diastolic function seems to be related to the ischaemic time of the donor heart and to a mismatch between the size of the donor heart and the recipient's needs.

Cardiac transplantation and heart-lung transplantation have become an accepted treatment for end stage cardiac and cardiopulmonary disease.[1–6] The exercise capacity of transplant recipients is good, but less than that of normal subjects.[7–10] Its contractile state and contractile reserve have also been shown to be normal.[11 12] In contrast with systolic function there is increasing evidence of impaired diastolic function after cardiac transplantation.[13–15]

We have analysed the diastolic function in the transplanted heart. Three major components of diastole were analysed: *synchrony* of left ventricular relaxation,[16–19] duration of left ventricular *relaxation*,[20–23] and left ventricular *passive diastolic properties*.[24–27] Furthermore, the relation between certain variables such as ischaemic time of the donor heart,[28–30] number of rejection episodes, type of immunosuppression,[31–32] and diastolic function were studied.

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Patients and methods

All studies were performed during routine yearly follow up cardiac catheterisations after cardiac or heart-lung transplantation.

PATIENTS

Thirty two transplanted patients were studied. Twenty four patients underwent cardiac transplantation and eight patients heart-lung transplantation. Preoperative diagnosis before cardiac transplantation was cardiomyopathy in 16 patients and ischaemic heart disease in eight patients. The heart-lung transplantation group was made up of five patients with primary pulmonary hypertension, two patients with Eisenmenger's syndrome caused by congenital heart disease, and one patient with cystic fibrosis. Immunosuppression consisted of treatment with cyclosporin and azathioprine in 23 transplanted patients,[33] steroids and azathioprine in four patients with transplants, and all three drugs (cyclosporin, steroids, and azathioprine) in two patients with transplants. Two patients were treated with cyclosporin alone and one with azathioprine alone, so only five patients were not treated with cyclosporin. All other medications were stopped 24 hours before the study. None of the patients received drugs likely to alter diastolic function (such as β blockers or calcium antagonists). Tables 1–3 give patient data.

CONTROL GROUPS

Patients with transplants were compared with controls with normal cardiac anatomy and left ventricular function. Three control groups (control groups 1 a to c) were used because it was impossible to perform all measurements of diastolic function in each of the controls. The control groups consisted of individuals who had diagnostic cardiac catheterisation for atypical chest pain or suspected congenital heart disease. All were in sinus rhythm and were found to have angiographically normal coronary arteries and structurally normal hearts. There were 12 in control group 1a from which normal values for the time constant of isovolumic pressure decay and cycle efficiency were obtained. Control group 1b consisted of 20 normal individuals from whom left ventricular angiograms were obtained by the same techniques as in the patients with transplants. From this control group we obtained normal values for the evaluation of left ventricular asynchrony. Control group 1c consisted of 10 normal individuals from whom we obtained normal values for passive diastolic properties.

METHODS

Cardiac catheterisation

In all patients with transplants coronary angiograms were performed and multiple (usually three) endomyocardial right ventricular biopsy specimens were obtained from the femoral approach. None of the patients showed cardiac allograft rejection according to criteria defined by Billingham and Griffith *et al.*[34,35] No attempt was made to quantify myocardial fibrosis, as this might have been influenced by the presence of scar tissue from previous biopsies.

Table 1 *Patient data*

	Total group (no)	*Cardiac transplants (no)*	*Heart-lung transplants (no)*
Recipient age (yr):			
<18	6	3	3
18–30	9	5	4
31–40	2	1	1
41–51	11	11	—
>51	4	4	—
Donor age (yr):			
<16	10	6	4
16–20	10	9	1
21–25	8	6	2
26–30	3	2	1
>30	1	1	—
Time since transplantation (yr)			
1	15	8	7
2	9	8	1
3	5	5	—
>3	3	3	—

Table 2 *Interval between cross clamping of the aorta in the donor and reperfusion in the recipient*

Ischaemic time (h)	*Total group (no)*	*Cardiac transplants (no)*	*Heart-lung transplants (no)*
<1	1	—	1
1·0–1·5	3	3	—
1·5–2·0	6	4	2
2·0–2·5	7	5	2
2·5–3·0	6	4	2
3·0–3·5	4	3	1
3·5–4·0	4	4	
>4·0	1	1	

Angiograms and endomyocardial biopsies were postponed until the measurements for the evaluation of relaxation, cycle efficiency, and passive diastolic filling were completed. High fidelity left ventricular pressure recordings were obtained with micromanometer-tipped 4F fibreoptic catheters (Camino Laboratories, model 110-4). The high fidelity catheters were balanced and electronically calibrated immediately before insertion and after withdrawal. No significant baseline shift occurred during the recording period.

Time constant of isovolumic pressure decay

For calculation of the time constant of isovolumic pressure decay left ventricular pressure tracings (paper speed 200 mm/s) were manually digitised with an electronic digitiser. The first derivative of the left ventricular pressure curve (dP/dt) was obtained by digital differentiation with a Cardio 200 computer (Kontron Image Analysis). For calculation of the time constant of isovolumic pressure decay the isovolumic relaxation period was defined as the interval between the minimum value for the first derivative of the left ventricular pressure (dP/dt_{min}) and the time when the pressure returned to the end diastolic pressure (LVEDP) of the preceding cardiac cycle.[16,20–23] A monoexponential model with asymp-

Table 3 *Increased number of rejection episodes**

	Total group	*Cardiac transplants*	*Heart-lung transplants*
First 3 months	9 of 32	7 of 24	2 of 8
3 months to 1 year	5 of 32	4 of 24	1 of 8
2nd year	4 of 14	4 of 13	None
>2nd year	None	None	None

Histological grading of rejection.[34,35]

*Three rejection episodes during the first three months after transplantation, two rejection episodes during the subsequent nine months, and one rejection episode yearly thereafter were arbitrarily defined as "normal"; the table gives the number of rejection episodes beyond these normal estimates.

tote was used to calculate the time constant of isovolumic pressure decay T: $P(t) = a * e^{b*t} + C$, where P(t) is instantaneous LV pressure; t is time; a and b are constants; and C is the asymptote. The time constant T of isovolumic pressure decay is defined as: $T = -1/b$, where T was calculated by iteration by the least squares method (best fit).

Echocardiograms

M mode echocardiograms of the left ventricle were recorded in patients in the supine position at the tip of the mitral valve leaflets with a 3·5 MHz or 2·25 MHz transducer and an Ekoline 20A echocardiograph (Smith-Kline Instruments). Left ventricular pressure was recorded simultaneously as mentioned above. The recordings were made at a paper speed of at least 100 mm/s.

Cycle efficiency

Pressure-dimension loops were constructed from the left ventricular internal dimension and the instantaneous left ventricular pressure as originally described by Gibson and Brown.[17 18] Cycle efficiency was defined as the ratio of the area within the pressure-dimension loop and that of the rectangle that encloses it.[17 18]

Assessment of left ventricular asynchrony

Left ventricular asynchrony was assessed through frame by frame analysis of left ventricular angiograms.[16] No extrasystoles or postextrasystoles were analysed. Left ventricular angiograms were performed in the right anterior oblique position at a frame rate of 50 frames/s after pressure recordings and echocardiograms were completed.

Frame by frame analysis of regional wall motion was performed from the digitised ventriculograms by a Cardio 200 computer (Kontron Image Analysis). Regional wall motion was analysed by a polar coordinate system with 24 segments (fig 1). No superposition was performed (fixed reference system). Regions adjacent to the mitral valve were excluded from analysis. Regional changes in area were calculated for each segment frame by frame. The delay between minimum cavity dimension and minimal segment area was calculated for each segment and the standard deviation of these intervals was defined as the "index of left ventricular asynchrony."

Evaluation of left ventricular passive diastolic properties

Passive viscoelastic diastolic properties were evaluated by simultaneous recording of the M mode echocardiograms and left ventricular diastolic pressure. From the digitised M mode echocardiograms the instantaneous internal left ventricular dimension ($D_i(t)$), posterior wall thickness (h(t)), midwall left ventricular circumference (l(t)), and the first derivative of the midwall left ventricular circumference (dl/dt) were obtained. The circular shape of the left ventricular short axis was confirmed by cross dimensional echocardiography. For the calculation of chamber stiffness and myocardial stiffness the time interval between minimum diastolic pressure and end diastolic pressure was analysed. Passive diastolic properties were analysed at end expiration. The stiffness of the left ventricular chamber and myocardium was calculated according to the method described by Hess *et al*[27] (appendix A).

STATISTICAL ANALYSIS

We used Student's *t* test for unpaired data to compare patients with transplants and controls. Simple, partial, and multiple regressions were used to analyse the influence of specific variables such as ischaemic time and donor age on diastolic function. A p value of <0.05 was regarded as statistically significant.

Results

STANDARD HAEMODYNAMIC DATA

Table 4 shows the standard haemodynamic data obtained during diagnostic cardiac catheterisation in patients with transplants and in controls. The heart rate was significantly lower in control group 1c ($p < 0.001$) than in the patients with transplants. Left ventricular systolic and end diastolic pressure, end diastolic volume, and ejection fraction did not differ between the groups.

CYCLE EFFICIENCY

Although cycle efficiency was slightly lower in the patients with transplants, there was no significant difference compared with the control group (table 5). Cycle efficiency was significantly greater after heart-lung transplantation than after cardiac transplantation ($p < 0.05$). After cardiac transplantation cycle efficiency was slightly less than in controls ($p < 0.05$) (table 5).

Regression analysis showed a significant inverse relation between recipient age and cycle efficiency in all patients with transplants ($r = -0.457$; $p < 0.01$). No significant correlation between recipient age and cycle efficiency could be shown in the cardiac transplant group ($r = -0.327$; NS).

INDEX OF LEFT VENTRICULAR ASYNCHRONY

No difference in the synchrony of the onset of relaxation was noted between any of the groups (table 5). Asynchronous onset of relaxation was seen in only two cardiac transplant patients (fig 2). We saw no

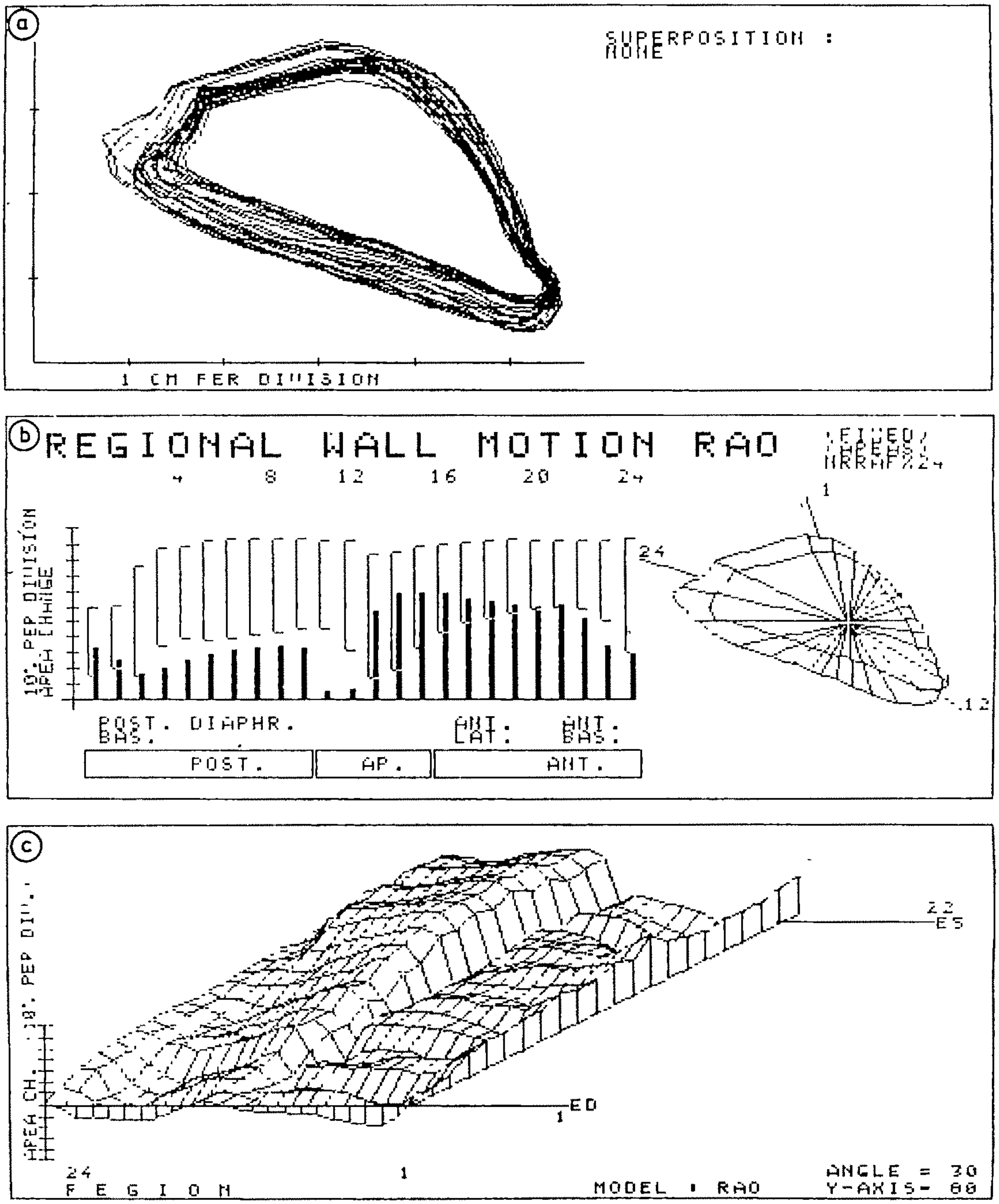

Fig 1 *Assessment of left ventricular asynchrony after cardiac and combined heart and lung transplantation. (a) Regional wall motion was analysed from left ventricular contours digitised frame by frame by (b) a polar coordinate system with 24 segments without superposition (fixed reference system). The delay between minimum cavity dimension and minimal segment area was calculated for each segment and the standard deviation of these time intervals was defined as the index of left ventricular asynchrony.*[16] *The three dimensional display shows the percentage area change (z axis) for each frame (y axis) and segment (x axis) graphically.*

Table 4 *Standard haemodynamic variables (mean (SD))*

	Total group	*Cardiac transplants*	*Heart-lung transplants*
No	32	24	8
HR	89 (13)	86 (10)	97 (8)**
EF	68 (9)	68 (9)	69 (7)
LVSP	122 (15)	121 (12)	126 (14)
LVEDP	10 (4)	10 (4)	10 (3)
LVEDVI	80 (7)	82 (6)	74 (9)
	Control group 1a	*Control group 1b*	*Control group 1c*
No	12	20	10
HR	83 (9)*	85 (7)**	71 (4)***
EF	71 (4)	71 (5)	69 (2)
LVSP	128 (11)	124 (7)	117 (3)
LVEDP	7 (3)	7 (3)	8 (1)
LVEDVI	81 (9)	83 (7)	85 (7)

HR, heart rate; EF, left ventricular ejection fraction; LVSP, left ventricular peak systolic pressure, LVEDP, left ventricular end diastolic pressure; LVEDVI, left ventricular end diastolic volume index.
Heart-lung transplantation group *v* control group 1a, *p < 0 05; *v* control group 1b, **p < 0 01; and *v* control group 1c, ***p < 0 001. Control group 1c *v* patient groups, ***p < 0·001. Pressure measurements were performed with fluid filled catheters during diagnostic cardiac catheterisation.

differences between those patients who underwent cardiac transplantation and those who underwent heart-lung transplantation.

Regression analysis showed a modest influence of the ischaemic time and recipient age on the index of left ventricular asynchrony (multiple correlation: $r = 0{\cdot}399$; $p < 0{\cdot}05$). Simple correlations were not significant (recipient age *v* index of asynchrony, $r = 0{\cdot}164$; ischaemic time *v* index of asynchrony, $r = 0{\cdot}317$).

TIME CONSTANT OF ISOVOLUMIC PRESSURE DECAY (T)

T was normal in patients with transplants (table 5, fig 2); it was significantly prolonged in only two patients with transplants.

LEFT VENTRICULAR CHAMBER STIFFNESS

Although the constant of left ventricular chamber stiffness b_C (see appendix A) was increased in seven of the patients with transplants (fig 3), mean values for patients with transplants and controls did not differ significantly (table 6; fig 3). In addition, the elastic constant a_C of the pressure-circumference relation and the constant of left ventricular chamber viscosity v_C were similar in both groups (table 6). Figure 4 shows the "averaged" pressure-circumference and stress-strain curves.

Regression analysis showed a significant influence of ischaemic time ($r = 0{\cdot}410$; $p < 0{\cdot}05$) and donor age ($r = -0{\cdot}381$; $p < 0{\cdot}05$) on the constant of left ventricular chamber stiffness b_C (multiple correlation $r = 0{\cdot}530$; $p < 0{\cdot}003$). An influence of donor age on b_C could also be shown in cardiac transplant patients ($r = -0{\cdot}404$; $p < 0{\cdot}05$).

Table 5 *Cycle efficiency, index of left ventricular asynchrony, and time constant of isovolumic pressure decay after cardiac and heart-lung transplantation (mean (SD))*

	Cycle efficiency (%)	*Index of asynchrony (ms)*	*T (ms)*
Total group (32)	77 8 (8 9)	25·8 (12)	44·3 (11·2)
Cardiac (24)	75 9 (9 4)*	26·5 (8·7)	45·3 (9·1)
Heart-lung (8)	83 6 (3 4)**	24·5 (8 6)	41·6 (8 7)
Control group	82·1 (5·1)	23·6 (9 5)	47·1 (12·9)

*Cardiac transplants *v* control group, p < 0 05; **cardiac transplants *v* heart-lung transplants, p < 0 05.

LEFT VENTRICULAR MYOCARDIAL STIFFNESS

The reference midwall circumference L1 was identical in controls and those with transplants (table 6). Both the constant of left ventricular myocardial stiffness b_M ($p < 0{\cdot}02$) and the elastic constant a_M ($p < 0{\cdot}002$) of the stress-strain relation were significantly increased in patients with transplants (table 6). The constants a_M and b_M were increased particularly after cardiac transplantation ($p < 0{\cdot}001$ and $p < 0{\cdot}01$, respectively). These indices were not significantly increased after heart-lung transplantation (table 6, fig 3). Myocardial stiffness b_M was increased in only one heart-lung transplant (fig 3); this, however, increased the standard deviation substantially so that no significant difference between the two patient groups could be shown. The constant of left ventricular myocardial viscosity (v_M) was similar in all groups.

As with chamber stiffness, regression analyses

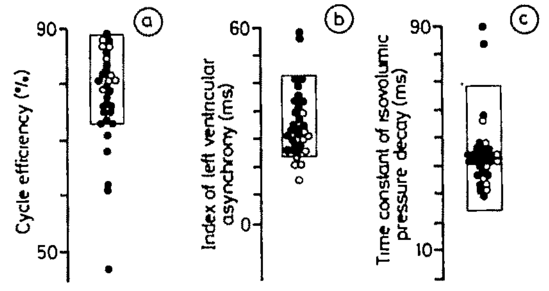

Fig 2 *Individual data and corresponding normal ranges (mean (SD) for cycle efficiency, index of left ventricular asynchrony, and time constant of left ventricular pressure decay. Solid circles indicate cardiac transplant patients, open circles indicate heart-lung transplant patients. Cycle efficiency was significantly reduced after cardiac transplantation (p < 0 05), while it was normal after heart-lung transplantation. The index of left ventricular asynchrony and the time constant of left ventricular pressure decay were normal after cardiac and heart-lung transplantation.*

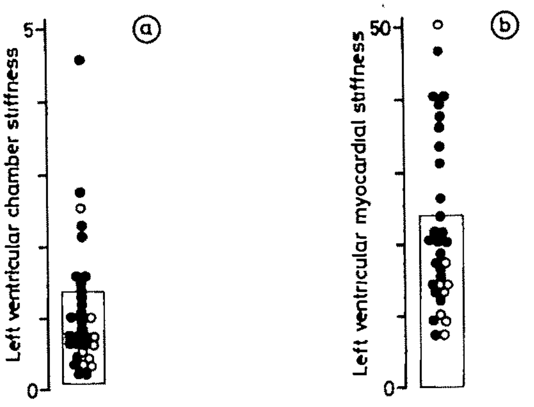

Fig 3 *Individual data and corresponding normal ranges (mean (SD)) of left ventricular chamber stiffness (b_C) (a) and left ventricular myocardial stiffness (b_M) (b) are shown. Solid circles are patients after cardiac transplantation and open circles indicate patients after combined heart and lung transplantation. The constant of left ventricular myocardial stiffness b_M was significantly increased in the whole group ($p < 0.02$) and especially after cardiac transplantation ($p < 0.01$), while the constant of left ventricular chamber stiffness b_c did not differ significantly from the control group. After heart-lung transplantation only one patient showed an increased chamber and myocardial stiffness.*

showed a significant correlation between the constant of left ventricular myocardial stiffness b_M and both ischaemic time and donor age (multiple correlation $r = 0.402$; $p < 0.05$). Simple correlations were not significant (ischaemic time *v* constant of myocardial stiffness b_M: $r = 0.196$; donor age *v* constant of myocardial stiffness b_M: $r = -0.326$).

CORONARY ANGIOGRAMS

Yearly follow up coronary angiograms showed normal coronary arteries in 24 patients with transplants, mild atherosclerotic plaques in six patients with transplants, and slight (<30%) coronary stenoses in two patients with transplants. Significant coronary stenoses were not seen in any of the patients studied.

ENDOMYOCARDIAL BIOPSIES

Endomyocardial biopsy specimens showed no evidence of cardiac allograft rejection in any of the patients with transplants.

Discussion

Although a transplanted heart comes from a young donor without evidence of preexisting cardiovascular disease, its later function could be influenced by the brain death of the donor,[30] as well as by impaired haemodynamic function and cardiovascular disease of the donor.[28 29] Additional mechanisms that could potentially alter the performance of the cardiac allograft are ischaemia during harvesting and transport of the donor heart,[28-30] acute allograft rejections, insidious chronic rejection,[4-6 11] denervation of the donor heart, specific fibrosis caused by cyclosporin,[15 31 35] and possible recurrence of original disease in the recipient.

EVALUATION OF ALTERED DIASTOLIC FUNCTION AFTER CARDIAC TRANSPLANTATION

While systolic function, as assessed by afterload increment, and the contractile reserve of the cardiac allograft were almost normal,[12] diastolic function was abnormal. Our data showed an increase in myocardial stiffness, a small but insignificant increase in left ventricular chamber stiffness, and a slight reduction of cycle efficiency after cardiac transplantation (figs 2 and 3).

Diastolic function was almost normal after heart and lung transplantation (figs 2 and 3); left ventricular chamber stiffness and myocardial stiffness were increased in only one heart-lung transplant patient. This could be the result of differences in

Table 6 *Left ventricular chamber stiffness and myocardial stiffness after cardiac and combined heart-lung transplantation (mean (SD))*

	Chamber stiffness				*Myocardial stiffness*		
	a_C	b_C	v_C	*L1*	a_M	b_M	v_M
Total group	0·020 (0·043)	1·12 (0·92)	0·03 (0·11)	14·2 (3·57)	0·41* (1·05)	21·2⁺ (12·5)	0·62 (1·03)
Cardiac transplants	0·022 (0·031)	1·22 (0·84)	0·02 (0·11)	14·5 (4·21)	0·29** (0·93)	22·1⁺⁺ (11·3)	0·54 (1·04)
Heart-lung transplants	0·013 (0·021)	0·82 (0·73)	0·05 (0·12)	13·2 (2·62)	0·75 (4·32)	18·5 (17·8)	0·69 (0·79)
Control group	0·007 (0·098)	0·73 (0·36)	0·03 (0·12)	14·2 (3·09)	1·6 (0·71)	11·1 (6·8)	0·85 (2·21)

a_C = elastic constant; b_C = constant of chamber stiffness; v_C = = viscoelastic constant; L1 = reference length for calculation of strain; a_M = elastic constant; b_M = constant of myocardial stiffness, v_M = viscoelastic constant.
$^{**}p < 0.001$, $^{*}p < 0.002$, $^{++}p < 0.01$; $^{+}p < 0.02$ compared with control group.

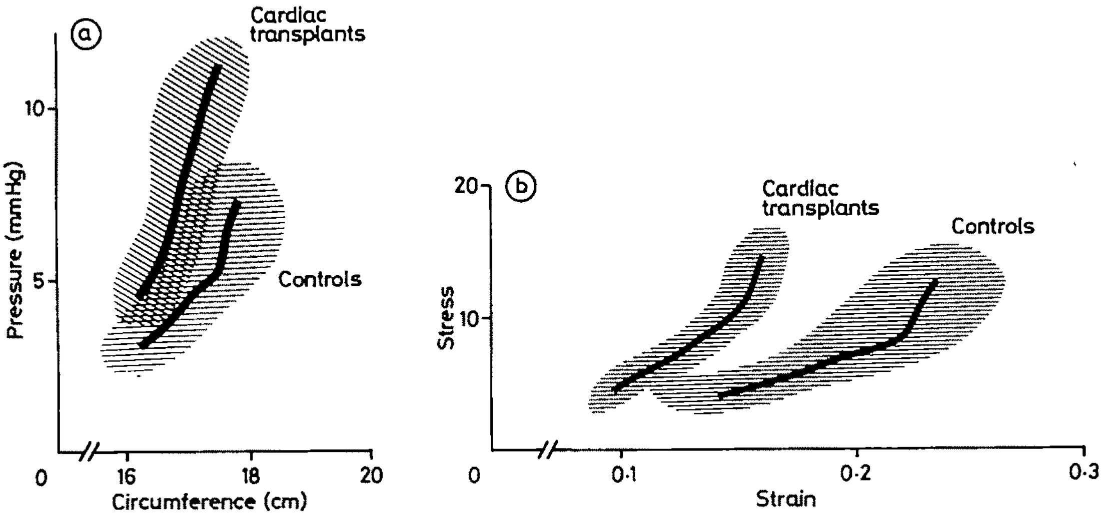

Fig 4 *Averaged pressure-circumference (a) and stress-strain (b) relations in controls and after cardiac transplantation. The individual pressure-circumference and stress-strain curves from each patient were divided into 28 discrete points and these were averaged to obtain averaged pressure-circumference and stress-strain curves. The figure shows these averaged pressure-circumference and stress-strain curves with the corresponding standard estimate of the mean. The averaged pressure-circumference and stress-strain curves of the heart-lung transplant patients were no different from those for the control group (data not shown).*

myocardial protection: in cardiac transplantation crystalloid cardioplegia was performed but for heart-lung transplantation the donor was cooled and blood cardioplegia was performed.[36] Another explanation is the possible immunological protection of the heart by the lungs.

Others have questioned whether the passive diastolic properties of the myocardium are best represented by a viscoelastic model,[37] but these theoretical considerations should be of no importance in our study because we saw no differences in the viscoelastic constant between any of the groups. The method reported by Hess *et al* was used to evaluate passive diastolic filling, because this method correlated well with the extent of endomyocardial fibrosis.[27] Although no attempt was made to measure the extent of myocardial fibrosis in this study, these findings[27] suggest that increased myocardial stiffness reflects increased myocardial fibrosis. Other explanations such as incomplete relaxation[20 23] or considerable asynchrony of the onset of relaxation[16] could be excluded in our study, because both the time constant of isovolumic pressure decay and the index of left ventricular asynchrony were normal (fig 2).

Finally, steeper pressure-circumference and stress-strain curves could theoretically be caused by a leftward shift of these relations, with the left ventricle working on a steeper portion of the diastolic pressure-circumference and stress-strain curves. However, the reference length L1 was nearly identical in all groups, which rules out any such leftward shift (table 6, fig 4).

While cycle efficiency was reduced after cardiac transplantation (fig 2), indicating incoordinate contraction and relaxation, the index of left ventricular asynchrony was normal. Although the index of left ventricular asynchrony and cycle efficiency are both indicators of incoordination, they reflect different aspects of it. The index of left ventricular asynchrony reflects variability in timing of relaxation onset, while cycle efficiency is independent of timing but dependent on changes in left ventricular pressure and dimension. Cycle efficiency reflects changes in left ventricular shape during the isovolumic contraction and relaxation periods and therefore incoordinate contraction and relaxation.[17-19] Changes in left ventricular shape are usually also reflected by the "shape index" as originally described by Chen and Gibson.[38] In this group of patients with transplants the shape index was not analysed, because most left ventricular angiograms showed apical dyskinesia after the intraoperative use of an apical vent (fig 1); thus the shape index would have given unreliable results.[39] None the less, the reduction in cycle efficiency after transplantation cannot be explained by apical dyskinesia, because apical dyskinesia was seen after cardiac transplantation and heart-lung transplantation whereas cycle efficiency was normal after heart-lung transplantation.

The time constant of isovolumic pressure decay was normal in transplant patients. Therefore relaxation seems to be normal. This is of particular interest as relaxation is an active phenomenon that is modified by sympathetic innervation.[40,41] Although it has been suggested that incoordinate relaxation could affect the time constant of isovolumic pressure decay,[16] it can be shown mathematically that this is not the case (appendix B).

FACTORS PREDISPOSING TO DIASTOLIC DYSFUNCTION AFTER CARDIAC TRANSPLANTATION

Our data show that passive diastolic properties are significantly related to the ischaemic time of the donor heart, as is the index of left ventricular asynchrony. This finding accords with experimental findings.[30,31] Donor age showed an inverse relation with passive diastolic properties; this could be because of differences in the cause of death and clinical course among younger donors. In contrast with cardiac transplant patients, only one heart-lung transplant patient showed impaired passive diastolic properties (fig 3). This may be because of the different type of myocardial protection used. The donor heart of this particular patient had a relatively long ischaemic time (2·92 h) and was obtained from a 14 year old girl, while the recipient was a large 17 year old boy.

The indices of incoordinate relaxation correlated weakly with recipient age. Although for cycle efficiency this correlation was obviously the result of the younger age of heart-lung transplant patients (fig 2), this was not the case for the index of left ventricular asynchrony (fig 2). More patients are required to determine whether the relation between incoordinate relaxation and recipient age is the result of the recipient's underlying disease or is simply age related.

Diastolic dysfunction was not related to the interval between transplantation and study; this suggests that there was no progressive deterioration of diastolic function with time. No relation was seen between diastolic dysfunction and immunosuppression with cyclosporin. However, only five of the patients did not receive cyclosporin. Diastolic dysfunction seems to be unrelated to denervation, because diastolic function was almost normal after heart-lung transplantation.

The number of preceding rejection episoodes did not appear to influence diastolic function (table 3). This could be because rejection episodes in this group of transplanted patients were adequately treated. Evaluation of the effects of acute and chronic rejection, however, is extremely difficult if not impossible, because there is no way to measure exactly the severity or duration of rejection episodes.

This study confirmed the presence of diastolic dysfunction after cardiac transplantation. Impairment of diastolic function seemed to be the result of increased myocardial stiffness and a mild degree of incoordinate contraction and relaxation. Increased myocardial stiffness is related to the ischaemic time of the donor heart. There is a basic difference in diastolic properties in patients with heart-lung transplants and those with cardiac transplants. This could be the result of differences in organ preservation or harvesting and of immunological factors.

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Appendix A

Calculation of left ventricular chamber stiffness by an exponential model with a viscoelastic constant according to the method described by Hess *et al.*[27] It was calculated from the following equation:

$$P(t) = a_C{\star}e^{b_C{\star}l(t)} + v_C{\star}dl(t)/dt$$

where P(t) is left ventricular pressure; a_C is elastic constant; b_C is the constant of chamber stiffness; v_C is the viscoelastic constant, and l(t) is the left ventricular circumference.

The constants a_C, b_C, and v_C were calculated by use of the formula mentioned above by iteration so that the least squares estimate between the measured and calculated values was minimised.

Calculation of left ventricular myocardial stiffness—For calculation of left ventricular myocardial stiffness the stress-strain relations were analysed. Meridional wall stress (Str(t)) was calculated as:

$$Str(t) = 1{\cdot}35{\star}\frac{P(t){\star}D_i(t)}{4{\star}h(t){\star}(1 + h(t)/D_i(t))}\ [g/cm^2]$$

where Str(t) is meridional wall stress; P(t) is left ventricular pressure; $D_i(t)$ is left ventricular internal diameter; and h(t) is left ventricular posterior wall thickness.

For the calculation of strain (strain(t)) a reference length had to be defined. The reference midwall circumferance L1 was (arbitrarily) calculated for a meridional wall stress of 1 g/cm^2.[27] L1 was calculated by iteration of the following equation:

$$Str(t) = a{\star}e^{b{\star}l(t)} + v{\star}dl(t)/dt$$

Natural strain (E(t)) was calculated as:

$$E(t) = \ln(l(t)) - \ln(L1)$$

Myocardial stiffness was calculated by iteration of the following equation:

$$Str(t) = a_M \star e^{b_M \star E(t)} + v_M \star dE(t)/dt$$

where a_M is the elastic constant; b_M the constant of myocardial stiffness; and v_M the viscoelastic constant).

Appendix B

Two segments A and B with identical time constants of relaxation are analysed. Isovolumic pressure decay is assumed to be represented by a monoexponential model with asymptote. If segment B starts to relax the time interval $t^{\star}$ later than segment A, isovolumic pressure decay is expressed by:

$$\text{Segment A: } P_A(t) = a \star e^{b \star t} + c, \text{ and}$$
$$\text{Segment B: } P_B(t) = a \star e^{b \star (t + t^{\star})} + c$$

The resulting pressure P(t) from both segments can be expressed by:

$$\begin{aligned} 2 \star P(t) &= P_A(t) + P_B(t) \\ &= P_A(t) + P_A(t + t^{\star}) \\ &= [a \star e^{b \star t} + c] + [a \star e^{b \star (t + t^{\star})} + c] \\ &= [a \star e^{b \star t} + a \star e^{b \star t} \star e^{b \star t^{\star}}] + 2c \\ &= e^{b \star t} \star [a + a \star e^{b \star t^{\star}}] + 2c \\ P(t) &= [a/2 + a/2 \star e^{b \star t^{\star}}] \star e^{b \star t} + c \end{aligned}$$

because $t^{\star}$ is a constant time interval, $e^{b \star t^{\star}}$ is also constant; thus the resulting pressure P(t) can be expressed by:

$$P(t) = a^{\star\star} e^{b \star t} + c$$

While the time constant of this relation $T = -1/b$ remains constant with an asynchronous onset of relaxation, the constant $a = P(t_0)$ changes by the factor:

$$[1/2 + 1/2 \star e^{b \star t^{\star}}].$$

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Br Heart J 1989;62:133–9

Paediatric use of flecainide in supraventricular tachycardia: clinical efficacy and pharmacokinetics

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SUMMARY Twenty three children with recurrent supraventricular tachycardia were treated with flecainide. Twenty one of these received intravenous treatment during an attack (2 mg/kg over 10 minutes). The tachycardia was terminated in 17. After an intravenous bolus of flecainide, blood samples were drawn at regular intervals for analysis of flecainide concentration over 48 hours. Pharmacokinetic variables were calculated—median terminal half life 7·5 hours, median volume of distribution 6·2 l/kg, and median plasma clearance 7·2 ml/min/kg. There was a significant correlation between half life and age. Twenty of the children received long term treatment with an oral preparation of flecainide to prevent further attacks. Twelve had no further attacks and 16 were considered to have good control. Two children suffered potentially serious arrhythmogenic effects soon after the start of oral treatment and flecainide had to be stopped. During oral treatment regular blood samples were drawn and plasma concentrations were analysed to assess the therapeutic range. This did not differ substantially from that proposed in adults (400–800 μg/l). Eight children were electively withdrawn from oral flecainide to see whether they really needed it. Blood samples for measurement of flecainide concentration were drawn after their last oral dose. Pharmacokinetic variables were calculated: time to maximum concentration 2 hours, median terminal half life 7·9 hours. For the combined data from patients receiving intravenous and oral treatment there was a significant correlation between elimination half life and age. An intravenous dose of 2 mg/kg over at least 10 minutes and an initial oral dose of 6 mg/kg/day in three divided doses is recommended. Treatment should be started in hospital so that children in whom the drug may be arrhythmogenic can be identified and plasma concentrations measured to identify patients in whom lack of efficacy is caused by underdosage.

Flecainide is a new class Ic antiarrhythmic drug that has recently been introduced into paediatric practice. It acts on the fast sodium channel. It slows conduction throughout the conduction system and has its greatest effect on the His bundle. The refractory period of most tissues is only slightly prolonged except that of accessory pathways, where this effect is more pronounced.[1] In adults flecainide was highly effective in the treatment of both supraventricular and ventricular arrhythmias.[2] Side effects are not uncommon but are generally benign and dose dependent. However, flecainide, like other potent antiarrhythmic agents, may cause arrhythmogenic effects with potentially serious consequences.[3]

As with many new drugs flecainide has been given to children in doses modified from those that were successful in adult patients without examination of its pharmacokinetics in children.[4 5] A knowledge of the pharmacokinetics of flecainide in children may help to prevent unwanted effects of the drug and is essential if this potent drug is to be used to its full advantage in children.

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Table 1 *Patient characteristics*

Case	*Age*	*Sex*	*Diagnosis*	*Previous treatment*	*Cardiac diagnosis*	*Frequency*
1	7 day	M	HBT	dig, ado, ver	Myocardial necrosis	Incessant
2	8 day	F	AVRT/oc	ado	N	Daily
3*	1 mnth 7 day	M	AVRTc	ver, dis, amio	N	Daily
4	1 mnth 14 day	M	AVRTc	dig, ado, ver	N	1/week
5	1 mnth 15 day	F	AVRTc	dig, ado, ver	Multiple intracardiac tumours	4/week
6	1 mnth 17 day	M	AVRTc	dig, ver	N	Daily
7	2 mnth	M	AVNRT	dig, ado	TGA	Repetitive
8	2 mnth 2 day	M	AVRTc	dig, ado	N	Repetitive
9	2 mnth 7 day	M	AVRTo	dig, ver	N	1/week
10	3 mnth	F	AVRTc	dig	N	1/mnth
11	9 mnth 18 day	F	AVNRT	dig	N	1/mnth
12*	2 yr	F	A FL	dig, amio	ASD	Incessant
13*	3 yr	F	AVNRT	dig, prop	N	Repetitive
14	8 yr	F	AVRTc	ver, prop	N	6/mnth
15*	8 yr 8 mnth 15 day	M	AVNRT	dig, prop	N	5/yr
16	10 yr 9 mnth	F	AVNRT	dig, ver, prop	N	Daily
17	10 yr 10 mnth	F	AVRTc	dig, prop	N	1/mnth
18	10 yr 11 mnth	F	AVRTc	ver	N	5/yr
19*	11 yr 6 mnth	M	AVRTo	prop	N	2/yr
20	12 yr 3 mnth	F	AVRTo	dig, ver	VSD	1/mnth
21	12 yr 6 mnth	F	AVRTo	prop, nad	N	1/mnth
22*	13 yr 9 mnth	F	EAT	ver, dis	N	Incessant
23	17 yr	M	EAT	dig, ver	DILV	2/yr

*Patients reported in an earlier study[4]
HBT, His bundle tachycardia; AVRT, atrioventricular re-entry tachycardia; c, concealed pre-excitation, o, overt pre-excitation; AVNRT, atrioventricular nodal re-entry tachycardia; EAT, ectopic atrial tachycardia; A FL atrial flutter, dig, digoxin; ver, verapamil; ado, adenosine; prop, propranolol; dis, disopyramide; amio, amiodarone; nad, nadolol; TGA, complete transposition of the great arteries; ASD, atrial septal defect, VSD, ventricular septal defect; DILV, double inlet left ventricle, N, normal.

Patients and methods

Twenty three consecutive children with documented recurrent supraventricular tachycardia aged between eight days and 17 years (median two years) were treated with flecainide. Six of the children (patients 3, 12, 13, 15, 19, and 22 (table 1)) have already been reported by our group[4] in a study to assess efficacy of flecainide in terminating their acute arrhythmias. We have included them in the present study to report their pharmacokinetics and subsequent long term follow up. In most children the diagnosis could be made from analysis of the surface electrocardiogram during tachycardia and sinus rhythm. In nine of the children the diagnosis was confirmed by electrophysiological study. In total, 14 children had atrioventricular re-entry tachycardia—associated with overt pre-excitation in five and concealed in 9. Five had atrioventricular nodal re-entry tachycardia, two had ectopic atrial tachycardia, one His bundle tachycardia, and one atrial flutter. Seventeen of the children had structurally normal hearts. Of the other six, three had had operations for congenital cardiac anomalies: one an anatomical correction for atrioventricular concordance, ventriculo-arterial discordance (complete transposition); one a Kreutzer modification of the Fontan procedure for double inlet left ventricle, subpulmonary and pulmonary stenosis; and one closure of a ventricular septal defect (table 1). The infant with atrial flutter had an atrial secundum defect, the neonate with His bundle tachycardia had poor ventricular function and at necropsy was found to have widespread areas of myocardial necrosis of unknown cause, and one child with atrioventricular re-entry tachycardia had multiple intracardiac tumours. In all cases the attacks of tachycardia were recurrent or incessant and were refractory to conventional drug treatment. In 16 children the attack of supraventricular tachycardia that was treated intravenously occurred spontaneously; in five it was induced during an electrophysiological study. Children with evidence of sick sinus syndrome were excluded from the study as were children with evidence of clinical or biochemical renal or liver failure. Informed parental and, where appropriate, the patient's consent was obtained in each case and the ethics committees of both St George's and the Brompton Hospitals approved the trial.

METHODS

Flecainide (Tambocor, Riker Laboratories) was given intravenously at a dose of 2 mg/kg over 10 minutes during supraventricular tachycardia to 21 patients. The standard intravenous preparation of flecainide acetate (10 mg/ml) was used. Throughout drug administration the electrocardiogram was recorded and blood pressure monitored either by direct intra-arterial measurement or frequent sphygmomanometer readings. After drug administration blood samples (0·5 ml) were collected at regular intervals for 48 hours or until further episodes of tachycardia requiring treatment occurred. Where possible blood was sampled with a separate indwelling venous cannula. When this was not possible, in small neonates with difficult venous access, blood was sampled through the cannula used for intravenous drug administration, with vigorous flushing between samples. Plasma was then stored at −20°C before the measurement of plasma flecainide concentrations.

Oral flecainide was started in 20 patients at least 48 hours after the intravenous bolus for the prevention of recurrent attacks. Wherever possible standard tablets (100 mg) were used (that is if doses of 100 mg or 50 mg were required). These tablets are scored and can be halved easily. For the smaller children we used a liquid formulation of flecainide based on the intravenous preparation and prepared by the pharmacies of the Brompton and St George's Hospitals. Stability studies performed by Riker confirmed a stable formulation with a shelf life of at least three months. Oral medication was started in hospital. The dose used for long term treatment was the minimum required for suppression of arrhythmia during hospital stay or, if this could not be assessed because arrhythmia was infrequent, a dose required to achieve a pre-dose plasma flecainide concentration greater than 350 μg/l was used.

The children were then followed as outpatients and at each hospital visit attacks of tachycardia were documented, 12 lead electrocardiogram recorded, and a pre-dose blood sample collected for the measurement of plasma flecainide. If attacks were suspected, confirmation was sought with Holter monitor or Cardiomemo recordings and parents were encouraged to keep an accurate diary of events.

In a small group of children oral flecainide was electively withdrawn after long term oral treatment because it was no longer required. Blood samples were collected via an indwelling intravenous cannula at frequent intervals for 48 h after an oral dose of flecainide for the measurement of pharmacokinetic variables.

DRUG AND DATA ANALYSIS

Plasma flecainide concentrations were measured by high performance liquid chromatography.[6] Pharmacokinetic variables were derived from the computer program STRIPE.[7]

Results

INTRAVENOUS FLECAINIDE: EFFICACY

Two children did not receive intravenous treatment because their acute attack terminated spontaneously. Of the remaining 21 children, tachycardia was terminated in seventeen. The mean time to termination was 5·3 minutes (range 1·5–10 minutes). In the neonate with His bundle tachycardia flecainide resulted in a halving of the tachycardia rate with possible 2:1 exit block from the automatic focus eight minutes after the start of the flecainide bolus—a favourable result. In one child with atrioventricular re-entry tachycardia, one with ectopic atrial tachycardia, and another with atrial flutter, flecainide caused slowing of the tachycardia rate but failed to terminate the arrhythmia.

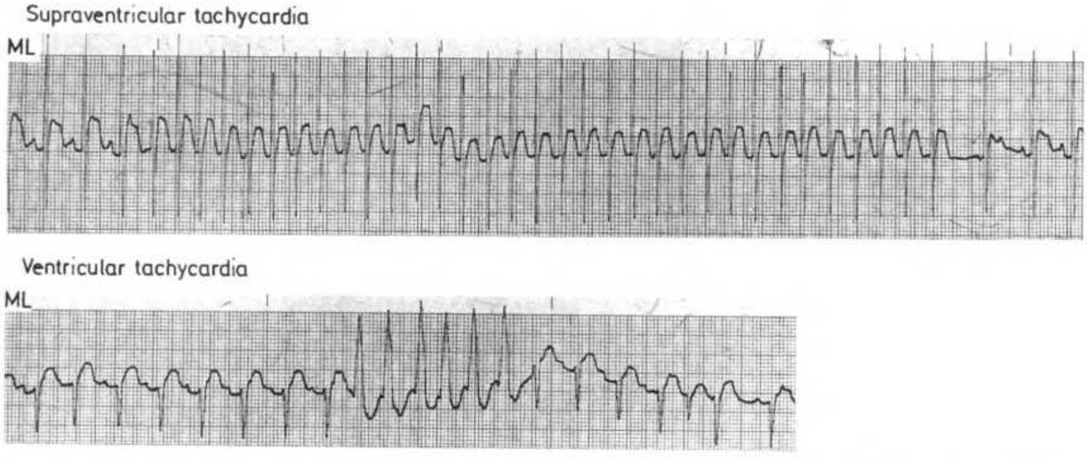

Fig 1 *Monitor lead from a neonate with atrioventricular nodal re-entry tachycardia. Monitor lead from the same neonate after treatment with flecainide showing non-sustained ventricular tachycardia—a possible arrhythmogenic effect of flecainide.*

Side effects during intravenous administration were few. The infant who had undergone anatomical correction suffered an episode of hypotension for 30–60 minutes during and after drug treatment. The systemic blood pressure fell 15 mm Hg (from 85 mm Hg to 70 mm Hg). No treatment was required for this and the blood pressure recovered spontaneously. Hypotension was not recorded in any other child during the study despite three other children being in severe cardiac failure (patients 1, 3, and 8) before flecainide was given. Two children reported a sensation of nausea and one vomited. These effects ceased within 15 minutes of drug administration.

Widening of the QRS complexes was seen after infusion, as expected from the known electrophysiological actions of the drug. No arrhythmogenesis occurred after intravenous flecainide.

ORAL FLECAINIDE: EFFICACY

Twenty of the 23 children received oral flecainide for long term control. Three children who had received intravenous flecainide did not enter this part of the study. The neonate with His bundle tachycardia, despite adequate control of heart rate, died with failing cardiac function two days after the intravenous dose of flecainide. Patient 2 had frequently recurring attacks of supraventricular tachycardia that were not terminated with intravenous flecainide. This child was not given a trial of oral flecainide because increasing cardiac failure necessitated more immediate treatment; intravenous amiodarone was finally successful in preventing further attacks. The third child who did not receive oral flecainide (patient 21) had in the past been partially controlled with nadolol and, despite rapid termination of arrhythmia with flecainide, her physician requested that she remain on nadolol.

In two patients flecainide had to be stopped shortly after oral treatment was started in hospital. In patient 8 oral flecainide was stopped after three days. This patient had responded well to intravenous flecainide but further administration of oral flecainide failed to prevent frequent attacks. The tachycardia rate slowed but remained incessant. Flecainide was therefore stopped and the attacks were later controlled with a combination of amiodarone and digoxin. Patient 7 developed episodes of ventricular tachycardia four days after oral treatment was started. These were of short duration and terminated spontaneously (fig 1). He was receiving a dose of 8·4 mg/kg/day and had a trough concentration of 570 μg/l. On withdrawal of flecainide his attacks of ventricular tachycardia resolved.

The remaining 18 children received long term oral flecainide. They have been followed up for 2–55 months (median 20 months). Twelve children have had no further attacks. Four others have been well controlled, with only one or two attacks of short duration per year. These attacks were often associated with failure to take medication. One child with atrioventricular re-entry tachycardia continued on oral flecainide for two months with poor control. However, no other agent could be found that achieved better control, and finally she underwent successful operation for resection of an accessory pathway when she was three months old. Of note are two children whose supraventricular tachycardia failed to stop in response to intravenous flecainide but who were well controlled, with no further attacks, when they were being treated with oral flecainide.

Long term pre-dose plasma flecainide concentrations associated with control varied from 170 to 935

Table 2 *Pharmacokinetic variables after intravenous flecainide (2 mg/kg)*

Case	*Age*	*Weight (kg)*	*Height (cm)*	*VSS (l/kg)*	*Total plasma clearance (ml/min/kg)*	*T½ elimination (h)*
1	7 day	2·7	49	8·5	48·2	3·8
3	1 mnth 7 day	4·5	56	6·7	6·7	10·1
4	1 mnth 14 day	4·3	55	—	—	5·4
7	2 mnth	2·8	52	8·2	18·9	5
8	2 mnth 2 day	3·8	51	9·0	9·2	11·6
10	3 mnth	6·0	62	6·7	10	7·5
13	3 yr	14·8	92	3·4	5·4	7·5
15	8 yr 8 mnth 15 day	37·0	146	1·9	3·0	7·2
16	10 yr 9 mnth	33·4	138	—	—	7·3
17	10 yr 10 mnth	30·0	143	5·7	7	9
18	10 yr 11 mnth	33·8	143	5	8·6	6·7
21	12 yr 6 mnth	47·6	153	4·7	6·6	8·2
22	13 yr 9 mnth	40·2	162	3·5	4·5	9·5
23	17 yr	50·0	176	6·8	7·4	10·6
Median	6 yr 4 mnth 15 day	25·7	118	6·2	7·2	7·5

The patient numbers correspond to those shown in table 1. VSS, volume of distribution at steady state; T½, half life.

Table 3 *Pharmacokinetic variables after the end of long term oral treatment*

Case	*Age*	*Wt (kg)*	*Ht (cm)*	*Surface area (m^2)*	*Total daily dose (mg)*	*Daily dose (mg/kg)*	*Daily dose (mg/m^2)*	*C max (μg/l)*	*T max (h)*	*Terminal elimination half life (h)*
5	1mnth 15 day	2·95	48	0·188	72	24	383	873	4·8	5·8
3	10 mnth	11·6	80	0·475	54	4·7	114	212	1	6·5
4	1 yr	11·1	77·5	0·455	54	4·9	119	228	4	4·8
11	1 yr 6 mnth	9·4	77	0·435	75	8·0	172	567	2	6
12	2 yr 6 mnth	9·3	76	0·425	50	5·4	118	400	1·3	9·2
14	8 yr	26·8	133	1·16	150	5·6	129	377	6	9·4
19	11 yr 6 mnth	46·6	152	1·38	200	4·3	145	558	2	9·6
18	13 yr	37·5	152	1·27	300	8·0	236	494	1	10·5
Median	2 yr	10·3	77·3	0·465	74	5·5	137	389	2	7·9

C max, maximum plasma concentration; T max, time to maximum plasma concentration. The patient numbers correspond to those shown in table 1

μg/l (median plasma concentration 415 μg/l). These corresponded to doses ranging from 3·6 to 11·1 mg/kg/day (median 4·8 mg/kg/day).

There were few side effects in the children on long term oral flecainide. One child developed a persistent severe headache two weeks after the start of treatment. This resolved after a reduction in dose. Plasma flecainide concentration at the time of the symptoms was 840 μg/l. No arrhythmogenic effects were noted in this group.

PHARMACOKINETICS AFTER INTRAVENOUS FLECAINIDE

Fourteen children completed this part of the study (table 2). In two cases (patients 4 and 16) the samples collected shortly after the infusion were inadvertently contaminated by intravenous flecainide preparation and these early data points could not be used for pharmacokinetic analysis. In the remaining cases there was a good fit between plasma flecainide concentration and time points.

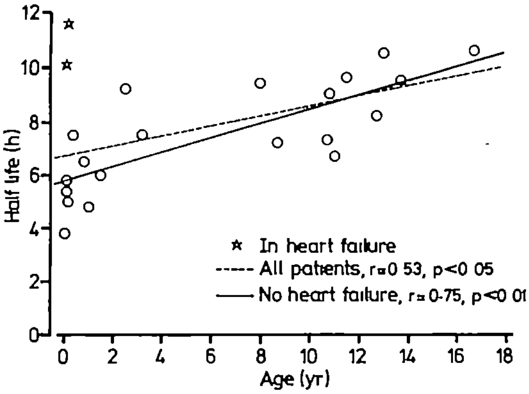

Fig 2 *Correlation between elimination half life and age for combined data on intravenous and oral treatment. The correlation was improved by the omission of data from two patients in heart failure.*

PHARMACOKINETICS AFTER THE END OF ORAL FLECAINIDE

Eight children underwent elective withdrawal of oral flecainide. Seven of the children had received flecainide for at least one year; one had received treatment for three weeks. Table 3 summarises the pharmacokinetic variables. Daily doses varied widely, both in relation to body weight and surface area. The correlation coefficients between maximum plasma concentration and daily dose calculated as either mg/kg or mg/m^2 were 0·57 and 0·70 respectively.

The median half life of elimination after the end of long term flecainide treatment was not significantly different from that calculated after short term intravenous dosing ($p < 0·1$, Mann-Whitney U test). For the combined data from patients receiving either intravenous or oral treatment there was a significant correlation between elimination half life and age ($r = 0·53, p < 0·05$) (fig 2). This correlation was improved if the data for the two patients who were in heart failure while they were treated with intravenous flecainide (patients 3 and 8) were omitted ($r = 0·75, p < 0·01$).

Discussion

Flecainide is a potent antiarrhythmic drug currently being used in children but the pharmacokinetics of flecainide in this age group have not yet been established.[5] Their elucidation may help to prevent some of the side effects and allow the drug to be used more successfully. Efficacy of intravenous flecainide in our group of patients with refractory tachycardia was high, in accordance with other studies. Termination of sustained tachycardia occurred in 17 of 21 cases. Side effects occurred in three of these children but in only one child was this a potentially serious problem. Plasma concentrations immediately after intravenous treatment were high. Administration over a longer period would reduce these concentrations and potentially reduce the incidence and severity of side effects.

Efficacy after oral treatment in this group of children with resistant tachycardia was also high. Twelve of 20 children had no further attacks while 16 had good control. Two children had potentially serious arrhythmogenic effects while on oral treatment. In common with other studies both arrhythmogenic events occurred soon after the start of oral treatment, supporting the practice of starting treatment in hospital. The frequency of arrhythmogenesis in our small group was high. In studies of adults arrhythmogenesis was more common in those patients with left ventricular dysfunction[8] and in those treated for ventricular arrhythmia.[9] The two children who had these effects in our group did not belong to either of these categories, nor was the concentration of flecainide in their plasma high at the time of arrhythmia. Arrhythmogenesis remains a worrying effect of the drug that should be watched for carefully.

It is difficult to assess accurately the plasma concentration of flecainide that was consistent with efficacy in our group of children because few suffered from incessant arrhythmia. However, we have no reason to conclude from this study that the target range for children differs substantially from that proposed in adult patients (that is 400–800 μg/l).

Compared with data obtained after the administration of flecainide to adult volunteers[10] or patients (data on file, Riker Laboratories Inc), our paediatric patient group showed a small decrease in the weight related volume of distribution of flecainide and a small increase in its total plasma clearance. The combined effect of these changes was to produce a considerable decrease in the elimination half life compared with adults and, clinically, this was the most important finding. There was a significant trend for the youngest children to have the shortest elimination half life. This was most noticeable if the data from the two patients in cardiac failure were omitted. Subsequent findings in one of these patients (patient 3) suggest that exclusion of these data is justified, because after oral treatment, when the patient was not in cardiac failure, the half life was considerably shorter and similar to the group median value.

On the basis of this study we recommend that an intravenous dose of flecainide of 2 mg/kg should be given over at least 10 minutes. In general an oral dose of about 6 mg/kg/day produces a plasma concentration within the therapeutic range accepted for adult patients and would be an appropriate starting dose. Higher doses may be required in small neonates and the use of plasma concentration measurements would help to identify cases in which lack of efficacy is the result of underdosage. Treatment should be started in hospital so that arrhythmogenic effects can be identified and dealt with swiftly. Flecainide is a drug with great potential for the treatment of childhood arrhythmias. A knowledge of the pharmacokinetics, with careful attention to optimum dosing, may contribute to its safe use in this age group.

We thank Riker Laboratories for supplies of flecainide and financial support and the staff of the pharmacies and paediatric wards at the Brompton and St George's Hospitals for their invaluable assistance.

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Addendum

Our study was undertaken before the preliminary results of the Cardiac Arrhythmia Suppression trial, by the National Heart Lung and Blood Institute in the United States, became known. As a result of the Cardiac Arrhythmia Suppression trial the Committee on Safety of Medicines in the United Kingdom has restricted the use of flecainide, at present, to life-threatening ventricular or junctional tachycardias. Our study, however, was of a very different population—children with supraventricular tachycardia—and there is no evidence that the results of the Cardiac Arrhythmia Suppression trial can be directly extrapolated to our population. Our patients will be followed as part of a prospective study on the safety of class Ic antiarrhythmic drugs in infants and children.

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Responsiveness of the ductus arteriosus to prostaglandin E_1 assessed by combined cross sectional and pulsed Doppler echocardiography

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SUMMARY Cross sectional echocardiography combined with Doppler echocardiography was used to record either ductal morphology or the flow profile within the ductus arteriosus before and after infusion of prostaglandin E_1 in 25 newborn infants with cyanotic and acyanotic congenital heart disease with ductus dependent blood flow. The ultrasound results were compared with changes in arterial oxygen tension and the overall clinical response to prostaglandin E_1 seen during the same period in 24 of the 25 patients in whom the degree of ductal narrowing could be determined with the ultrasound method. At the time of the study, the ductus was widely patent or slightly narrowed in 12 patients and was closed in two patients. These patients did not respond to prostaglandin E_1. There was prominent localised narrowing of the ductus in seven patients and generalised narrowing in three. After the infusion of prostaglandin E_1 there was no ductal narrowing in these patients, except for one patient who had slight residual localised narrowing. There was also a considerable change in the ductal flow profiles in each patient. In these 10 patients infusion of prostaglandin E_1 resulted in an increase in arterial oxygen tension, clinical improvement, or both.

The present study indicates that prostaglandin E_1 is effective in patients with prominent narrowing of the ductus but is not in patients in whom the ductus is widely patent or closed. Cross sectional echocardiography combined with Doppler echocardiography was useful for predicting the responsiveness of the ductus arteriosus to the infusion.

Since 1975, prostaglandins E_1 and E_2 have been used to maintain the patency of the ductus arteriosus in newborn infants with cyanotic and acyanotic congenital heart disease with ductus dependent blood flow.[1–6] The clinical effects of prostaglandins are variable. The factors that determine an infant's responsiveness to the infusion are not clear.

Clyman *et al* showed that in newborn lambs the absence of ductus responsiveness to prostaglandin E_2 was directly related to reduced luminal blood flow.[7] Recently, several investigators have shown that cross sectional echocardiography combined with Doppler echocardiography allows accurate assessment of both the shape of the ductus and the flow dynamics of the shunt in patients with the ductus arteriosus.[8–13] We therefore applied this technique to assess changes in the shape of the ductus arteriosus and the flow velocity profiles before and during prostaglandin E_1 infusion and to evaluate the difference between the group of patients who responded to the infusion and those who did not.

Patients and methods

Twenty five patients with congenital heart disease whose survival is dependent on ductal blood flow were evaluated prospectively between May 1985 and November 1987. All were treated with infusion of prostaglandin E_1 after cross sectional Doppler echocardiographic diagnosis before cardiac catheterisation. At the onset of infusion the infants were five hours to 35 days old (76% were <5 days old). Prostaglandin E_1 was infused at a dose of 0·05 to 0·1 μg/kg/min into a peripheral vein. The diagnosis was subsequently confirmed by angiography except for

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Table *Patient data*

			Cross sectional echocardiogram	
Patient No	*Diagnosis*	*Age (days) at PGE_1 infusion*	*DA shape*	*DA appearance before PGE_1*
Group 1 (ductus dependent pulmonary blood flow):				
1	TA (Ia)	4	T	Narrow PA end
2	TA (Ia)	0	T	Wide
3	TA (Ib)	0	T	Wide
4	PA, VSD	1	T	Narrow PA end
5	PPA	2	T	Narrow PA end and middle
6	PPA	1	C	Wide
7	PPA	0	C	Narrow middle
8	PPA	1	T	Narrow middle
9	Ebstein, PS	1	T	Narrow whole length
10	d-TGA, VSD, PS	2	T	Narrow PA end
Group 2 (ductus dependent systemic venous mixing).				
11	d-TGA (IVS)	1	C	Wide
12	d-TGA (IVS)	0	C	Wide
13	d-TGA (IVS)	1	C	Narrow PA end and middle
14	d-TGA (IVS)	0	C	Wide
15	d-TGA (IVS)	3	C	Narrow PA end
16	d-TGA (IVS)	0	C	Wide
17	d-TGA (IVS)	1	C	Narrow PA end
Group 3 (ductus dependent systemic blood flow):				
18	Coarctation	8	C	Narrow whole length
19	Coarctation, UVH	35	C	Narrow whole length
20	HPLHS	2	C	Wide
21	HPLHS	1	C	Wide
22	Coarctation, UVH	12	C	Wide
23	Coarctation	8	C	Closed
24	Coarctation, VSD	10	C	Closed
Group 4				
25	TAPVC (infra), ASD	1	C	Narrow middle

PGE_1, prostaglandin E_1; DA, ductus arteriosus, TA (Ia), tricuspid atresia with intact ventricular septum and pulmonary atresia; TA (Ib), tricuspid atresia with small VSD (ventricular septal defect) and pulmonary stenosis; PA, pulmonary atresia; PPA, pulmonary atresia with intact ventricular septum; PS, pulmonary stenosis; d-TGA (IVS), d-transposition of the great arteries (intact ventricular septum); coarctation, coarctation of the aorta; UVH, univentricular heart; HPLHS, hypoplastic left heart syndrome; TAPVC (infra), total anomalous pulmonary venous connection (infracardiac type); ASD, atrial septal defect; T, tortuous; C, cylindrical.

two patients with hypoplastic left heart syndrome, which was diagnosed by cross sectional echocardiography alone. The patients were divided into four groups (table). Group 1 consisted of 10 patients with ductus dependent pulmonary blood flow (simple or complex pulmonary atresia and critical pulmonary stenosis). Group 2 consisted of seven patients with ductus dependent systemic venous mixing (complete transposition of the great arteries with intact ventricular septum and atrial septal defect or persistent foramen ovale). Group 3 consisted of seven patients with ductus dependent systemic blood flow (coarctation of aorta and hypoplastic left heart syndrome). The only patient in group 4 had total anomalous pulmonary venous connection with venous obstruction in which the descending vein terminated in the hepatic vein, and with no other associated anomaly. In this patient, treatment with prostaglandin E_1 was started on the basis of Doppler determined ductal flow profiles and clinical deterioration. The efficacy of prostaglandin E_1 in the patients in groups 1 and 2 was assessed by changes in arterial oxygen tension. Arterial oxygen tension was usually measured immediately before and several times after the start of the infusion. When more than one value was obtained after the onset of the infusion, the value obtained closest to one hour after the start of the infusion was used for the analysis. The overall clinical effects of the infusion in the patients in groups 3 and 4 were evaluated by changes in blood pressure in the arms and legs, urine flow, and serial chest *x* ray films. In two infants with simple coarctation of the aorta, the systolic pressures in the femoral and radial arteries were monitored simultaneously throughout the period of infusion.

CROSS SECTIONAL AND DOPPLER ECHOCARDIOGRAPHIC STUDIES

All patients were studied with a pulsed Doppler echocardiographic system (Hewlett Packard, Model 77020 AC) with a 5 MHz shallow focus transducer immediately before and several times after the start of infusion of prostaglandin E_1. The data obtained closest to one hour after the start of the infusion were used to compare arterial oxygen tension values in patients in groups 1 and 2. For a high parasternal approach, the transducer was positioned in the second or third left intercostal space, rotated counterclockwise, and directed inferiorly or slightly superiorly. In this plane the ductus arteriosus was imaged above the junction of the left pulmonary artery with the main pulmonary trunk as reported previously.[13]

If this standard parasternal approach failed to visualise the ductus along its entire length we used another plane. The transducer was placed just below the right or left clavicle. Then it was rotated to visualise the long axis of the aortic arch—clockwise when the arch was left sided and counterclockwise when the arch was right sided. Next the transducer was directed inferiorly to visualise the ductus, the main pulmonary artery, and the aortic arch in the same cut.

Doppler interrogation was performed during simultaneous visualisation, with the sample volume placed in the middle of the ductus when it was widely patent and not tortuous, and at the pulmonary end, in the middle, and towards the aortic end when it was tortuous. Care was taken to place the sample volume at the same site in the ductus before and after the

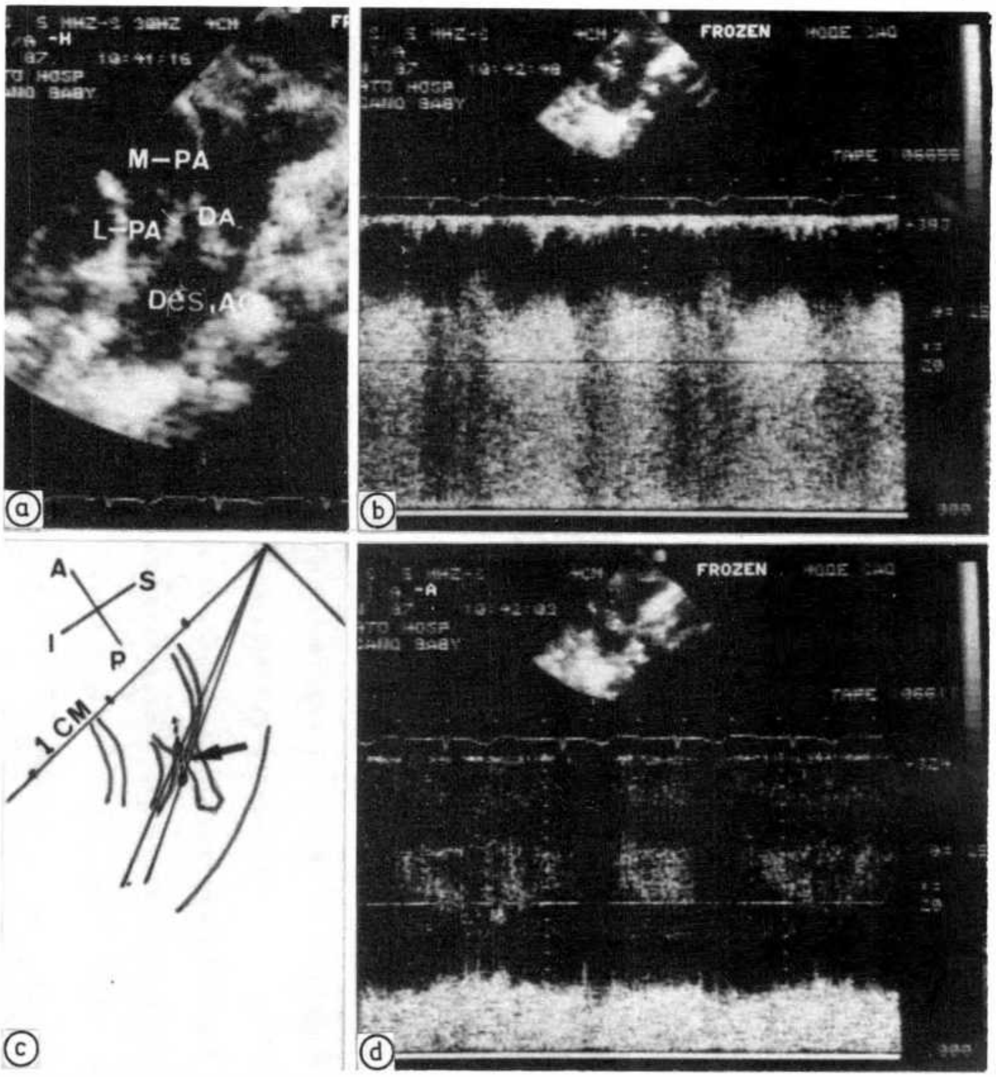

Fig 1 *(a and c) Long axis plane of the ductus showing localised narrowing in the middle (arrow). (b) Ductal flow profile indicating the left to right shunt flow of high velocity toward the transducer at a sampling site within the localised narrowing. (d) Non-phasic flow of low velocity upstream of the narrowing. Note the difference in flow velocity profile seen at two sampling sites within the ductus. A, anterior; P, posterior; S, superior; I, inferior; M-PA, main pulmonary artery; L-PA, left pulmonary artery; DA, ductus arteriosus; Des Ao, descending aorta.*

infusion of prostaglandin E_1. Previous reports of the closure process in normal newborn infants,[14] suggest that narrowing of the entire length of the ductus should be regarded as prominent when the ductus is <2 mm in diameter along its entire length. Similarly, we judged localised narrowing of the ductus to be prominent when the high velocity jet more than 2 m/s was directed superiorly from the localised narrowed portion of the ductus or if a characteristic non-phasic continuous flow of low velocity was recorded upstream from the narrowed portion at an intercept angle of $<50°$ or both (fig 1). We regarded other degrees of localised intraluminal narrowing on imaging to be slight. When no lumen was visible and Doppler showed no left to right shunting, closure of the duct was diagnosed. The Doppler profile and electrocardiograms were recorded simultaneously at 100 mm/s and stored on video tape for later analysis.

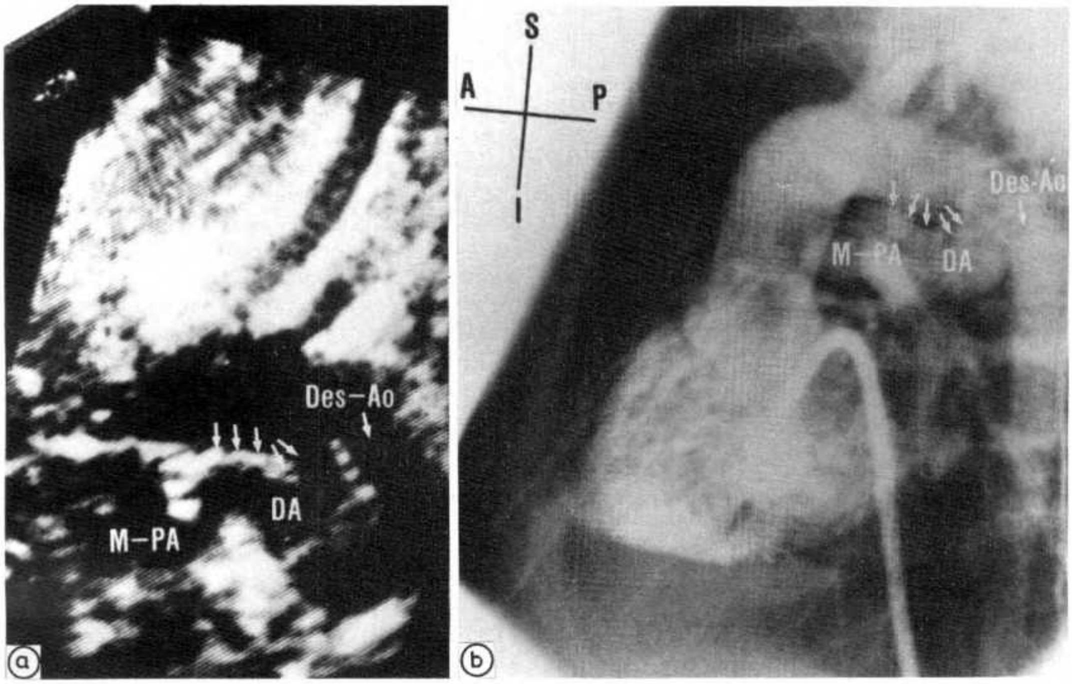

Fig 2 *(a) Cross sectional echocardiogram showing a tortuous ductus arteriosus (small arrows) in a patient with tricuspid atresia and pulmonary atresia with intact ventricular septum (type Ia). The window was obtained with a transducer just below the right clavicle. The widely patent ductus supplied the pulmonary arteries and formed an acute angle with the descending aorta. (b) The angiocardiogram for the same patient. See legend to fig 1 for abbreviations.*

Flow toward the transducer was displayed above the baseline, whereas flow away from the transducer was displayed below it.

STATISTICAL ANALYSIS

A two tailed Student's t test was used for statistical analysis of the difference of mean values between the two groups.

Results

DUCTAL MORPHOLOGY AND FLOW PROFILES BEFORE PROSTAGLANDIN E_1 INFUSION

The ductus could be clearly visualised along its entire length from a high parasternal approach in two planes in all patients except for two with a closed ductus, seven with a tortuous ductus in whom it was not possible to obtain an adequate imaging by the standard parasternal plane (fig 2), and two patients who had a cylindrical ductus. Ten patients had a ductus widely patent along its entire length, ranging from 3 to 7·5 mm (mean 5·3 mm) in the widest inner diameter. Of the remaining 13 patients with patent ducts, ductal narrowing was seen in the localised portion in 10 and along its entire length in three patients (table).

The Doppler method showed continuous left to right shunt flow within the ductus in all patients with ductus dependent pulmonary blood flow (group 1). A change in direction in the continuous velocity pattern was noted within tortuous ducts. In the other groups of patients with a patent ductus, ductal shunt flow profiles ranged from continuous left to right shunting to right to left shunting. In 14 of the 15 patients with a cylindrical ductus, the angle of intercept was $<30°$ within the ductus. In eight patients with a tortuous ductus the angle varied considerably with the sampling site in the ductus, but in seven patients it was $<50°$ at the aortic end, the pulmonary end, or both. This cross sectional and Doppler echocardiographic method showed that the degree of the ductal narrowing in a localised portion or along its entire length was prominent in 10 and mild in two; another patient had a localised narrowing and the ductus was almost vertically aligned with the Doppler cursor.

CLINICAL AND DUCTAL RESPONSIVENESS TO PROSTAGLANDIN E_1

In 16 of the 17 patients in groups 1 and 2 arterial oxygen tension was studied after prostaglandin E_1 infusion. A good clinical response, that is an increase in arterial oxygen tension of $\geqslant 10$ mm Hg, was noted

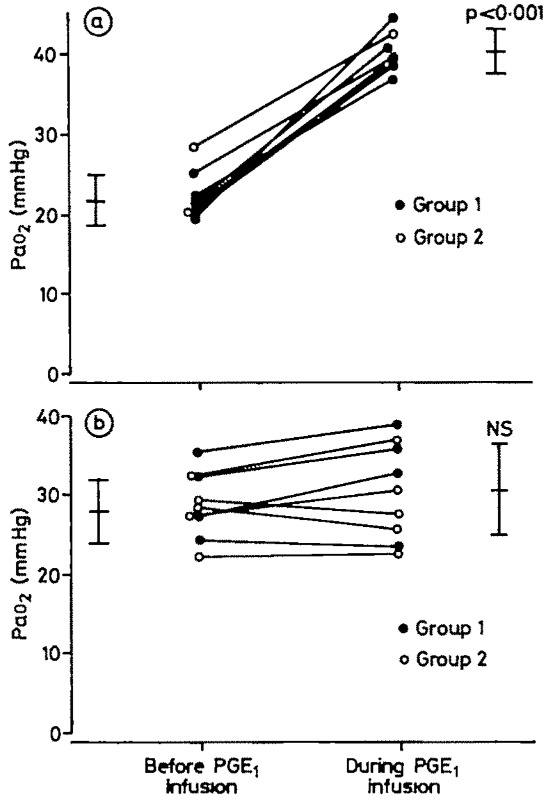

Fig 3 *Arterial oxygen tension (Pa_{O_2}) (mean (SD)) before and during infusion of prostaglandin E_1 in patients in groups 1 and 2. Note the difference in the response to prostaglandin E_1 between 7 patients with prominent narrowing of the ductus (a) and nine patients with slight narrowing of the ductus or a widely patent ductus (b).*

in only the seven patients in groups 1 and 2 who had prominent localised narrowing or narrowing along the whole length of the ductus before the infusion ($p < 0·001$) (fig 3a).

In all of these patients ductal narrowing on cross sectional and Doppler echocardiography disappeared after the infusion (fig 4). In contrast, the remaining nine patients who had a slightly narrowed or widely patent ductus did not show any significant change in arterial oxygen tension after the infusion (fig 3b). None of the 10 patients who had a widely patent ductus before and during the infusion showed a significant change in the widest ductal diameter. In two group 3 patients (cases 18 and 19) with coarctation of the aorta, the femoral artery pulse and urine flow improved during the infusion. In one patient the systolic pressure difference between radial and femoral arteries decreased from 55 to 30 mm Hg. In both patients the ductus was widely patent and the ductal flow profile changed from a right to left shunt to a bidirectional shunt after the infusion. In the other five group 3 patients, who had a widely patent or closed ductus, we saw no major changes in overall clinical findings after the infusion. In the two patients with a closed ductus, the ductus remained closed even when a high dose of prostaglandin E_1 (0·1 μg/kg/min) was given. In one patient (group 4) who had obstructive total anomalous pulmonary venous connection, the infusion resulted in an apparent improvement in pulmonary oedema on serial chest *x* ray films obtained 10 hours later and an increase in urine flow. This coincided with ductal dilatation and an increase in ductal right to left shunting (fig 5).

Discussion

In patients who did not respond to prostaglandin E_1, echocardiography combined with Doppler echocardiography showed that the ductus was widely patent or only slightly narrowed before prostaglandin E_1 infusion. Furthermore, the infusion had no effect on ductal diameter in any patient with a widely patent ductus. These data confirm the hypothesis that the diameter to which prostaglandin E_1 will dilate the ductus is limited.[5] In such patients, the infusion will not produce a further increase in oxygenation or clinical improvement, though it can be administered prophylactically to prevent ductal narrowing. Nor was prostaglandin E_1 effective in patients in whom the ductus was fully closed. But the infusion was very effective in patients in whom the ductus was patent with prominent localised or generalised narrowing. The ductus may remain responsive to prostaglandin E_1 as long as the ductus is not allowed to close fully before the infusion. The number of patients that we studied was too small to conclude that this outcome will always be achieved in such cases. Further study is needed to clarify this point.

In most of the patients with ductal narrowing, intraluminal changes were noted at a localised portion before the infusion. This localised narrowing was shown to be early evidence of ductal changes leading to spontaneous closure.[14] Cross sectional echocardiographic imaging alone provides important information of changes within the ductal lumen.[10 11 14] However, when the degree of localised narrowing is assessed by direct imaging the dimension of the narrowing in one plane cannot be used to assess the absolute size of the narrow portion and if the narrowed portion is < 2 mm in diameter it may fall outside the range of lateral resolution of the equipment being used. In the present study, the Doppler method could be used to confirm the ductal patency in patients with narrowing along the entire length of

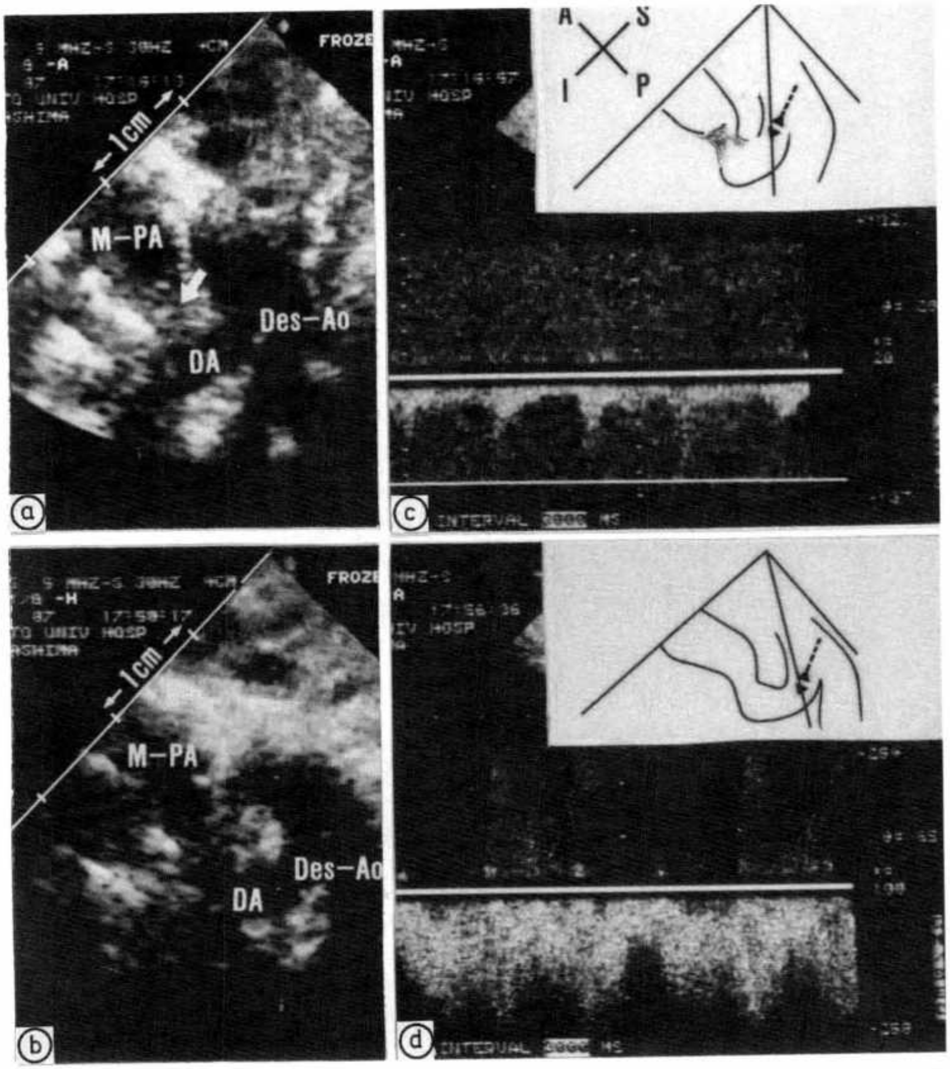

Fig 4 *Cross sectional echocardiograms and Doppler echocardiograms in a patient with pulmonary atresia and ventricular septal defect. (a) Localised narrowing (arrow) is indicated near the pulmonary end of the ductus before infusion of prostaglandin E_1. (b) The localised narrowing disappeared during the infusion. (c) Characteristic low velocity flow near aortic end of the ductus before the infusion. (d) A high velocity continuous flow away from the transducer at the same site as (c). The intercept angle was 30° in both panels. See legend to fig 1 for abbreviations.*

the ductus. This technique also provided additional information on the degree of the localised narrowing within the ductus. A high velocity jet was detected within and downstream from the narrowed portion. The flow velocity seen upstream of a localised narrowing was low and was usually non-phasic. Smallhorn and Freedom found that in patients with obstructive total anomalous venous connection the Doppler determined flow was non-phasic with a low velocity and turbulent with a high velocity, respectively, in the areas proximal and distal to the site of obstruction.[15] Thus the characteristic flow profiles seen in patients with prominent localised narrowing seem to reflect the actual narrowing within the ductus. But this Doppler approach is not accurate in patients in whom the ductus is imaged in a near vertical position to the Doppler cursor.

In two patients in group 3 with coarctation of the

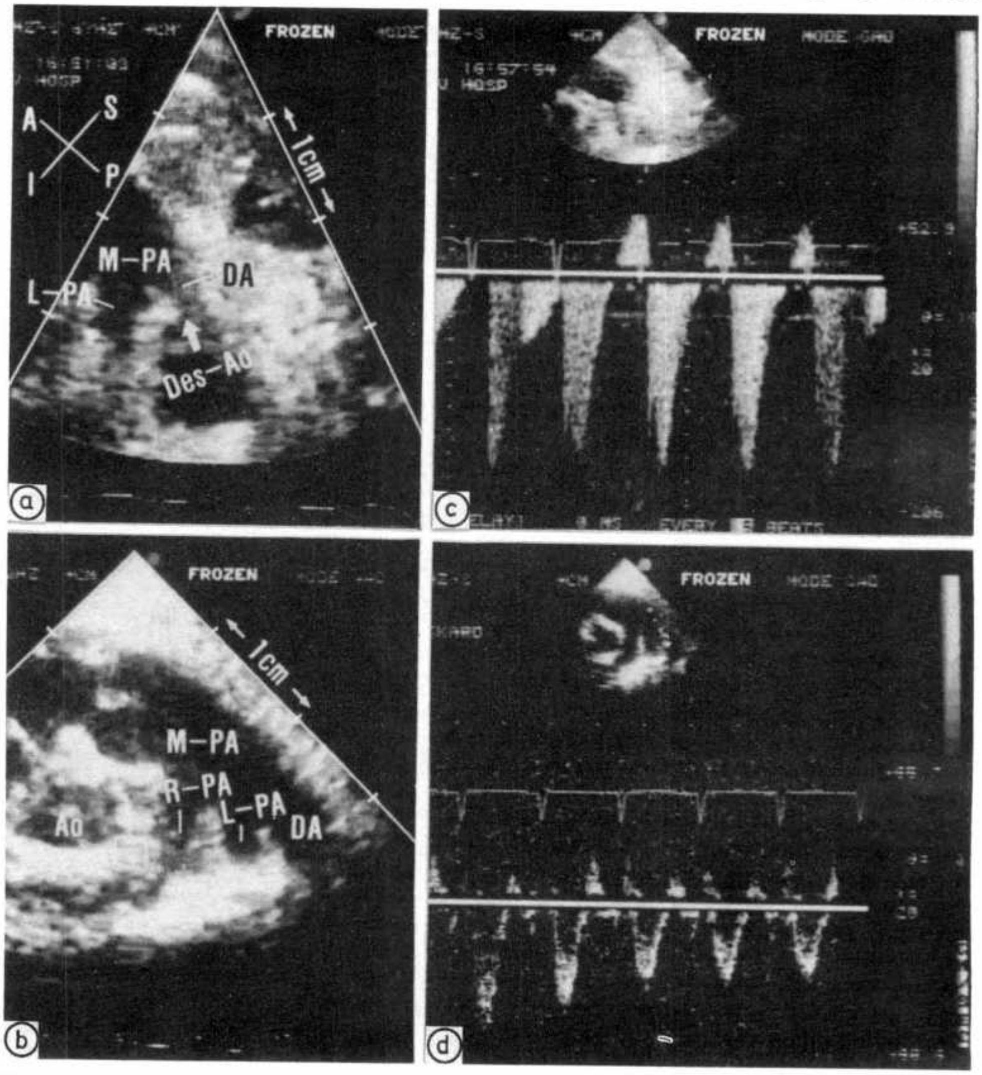

Fig 5 *Cross sectional echocardiograms and Doppler echocardiograms in a patient with obstructive total anomalous pulmonary venous connection. (a) Localised narrowing in the ductus (arrow) in its middle portion before infusion of prostaglandin E_1. (b) Ductus was widely patent during the infusion (c and d) Right to left ductal shunt flow away from the transducer was predominant before and during the infusion. Ductal dilatation resulted in laminar right to left ductal shunt flow. R-PA, right pulmonary artery; L-PA, left pulmonary artery; Ao, aorta; see legend to fig 1 for other abbreviations.*

aorta, a right to left ductal shunt became bidirectional after the infusion. This raises the possibility that the additional left to right shunt and diminished radiofemoral gradient are a consequence of diminished coarctation in such cases.

Freedom *et al* reported that prostaglandin E_1 infusion resulted in severe pulmonary oedema with considerable respiratory distress in one patient who had visceral heterotaxia, asplenia, and complex congenital heart disease including pulmonary atresia and an obstructive total anomalous pulmonary venous connection.[16] In the patient with obstructive total anomalous pulmonary venous connection and uncomplicated pulmonary outflow tract obstruction included in this study, the pulmonary oedema and urine flow improved within 10 hours of the infusion. The major change here may be that from a turbulent jet to a more laminar jet suggesting that a larger volume is passing through the ductus from the pulmonary artery to the aorta. Therefore, the difference in the clinical response to prostaglandin E_1 between Freedom's case[16] and ours seems to relate to the direction of shunt flow across the ductus and its flow volume, consequent on the presence or absence of pulmonary valve atresia.

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Balloon dilatation of congenital aortic valve stenosis in infants and children: short term and intermediate results

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SUMMARY Percutaneous balloon dilatation of the aortic valve was attempted in 25 consecutive patients with stenosis. The aortic valve diameters were normal for age. The balloon catheters were placed retrogradely, and their diameters were within 1–2 mm of the valve diameter and 3 (13 patients) or 6 cm (recent 12 patients) long. After dilatation the pressure gradients across the aortic valve were reduced significantly and the valve areas, measured in 10 patients, increased. Aortic regurgitation was detected in six patients before (grade I) the procedure and in 15 patients (6 grade I, 6 grade II, 3 grade III) after the procedure. In one patient the aortic valve could not be crossed and in three there was no reduction in the pressure drop. Nine patients have a sustained reduction in Doppler assessed gradients. There were vascular complications in 12 and these required surgical intervention in three patients.

Balloon dilatation seems to be an effective short term palliative procedure in patients with congenital stenosis of the aortic valve.

The success of balloon dilatation of the stenosed pulmonary valve,[1,2] has prompted the application of this technique to other heart lesions with varying success.[3-5] Its application to congenital valvar aortic stenosis is recent, and there are few clinical studies outlining the technique, complications, and patient tolerance.[6-9]

The purpose of this report is to outline the technique, complications, and short term results of balloon dilatation of the aortic valve and to examine short term follow up data on the gradient reduction and any improvement in ventricular function.

Patients and methods

CLINICAL DATA

From October 1985 up to and including March 1987 percutaneous balloon dilatation of congenitally stenosed aortic valves was attempted in 25 consecutive patients over six months of age (21 male, four female) (mean (SD) age 9·3 (5·4) (0·5–16·7) years and a mean (SD) body surface area of 0·87 (0·36) (0·3–1·4)m^2). In this period no patient had an operation as the initial form of management.

All patients had clinical and echocardiographic findings consistent with moderate to severe stenosis of the aortic valve[10]: 16 had an apical aortic click and in 18 there was a systolic ejection murmur associated with a precordial thrill. Six patients had a 1/6 early high frequency diastolic murmur of aortic regurgitation.

The mean (SD) cardiothoracic ratio on chest *x* ray was 0·5 (0·07) (0·43–0·7)%. Twenty one patients had evidence of left ventricular hypertrophy on the electrocardigram associated with ST segment inversion at rest in 11. Six patients underwent a graded exercise test protocol with a mean (SD) endurance time of 9·6 (1·7) (7–11) minutes with >2 mm ST-T wave depression as the end point. The mean echo-Doppler gradient was 71 (18) (40–100) mm Hg; the one patient with only a 40 mm Hg gradient was included in this study because of left ventricular strain on the electrocardiogram.

Two patients had previously undergone a sub-

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clavian flap angioplasty for repair of coarctation of the aorta; one had a supravalvar aortic ridge where the left aortic cusp had a superior attachment. Four patients had undergone previous open aortic valvotomy at a mean age of 8·8 (6) (1–14) years, a mean 3·3 (2·2) (0·5–8) years before balloon dilatation. These four had bicuspid aortic valves.

ECHOCARDIOGRAPHY

Cross sectional and Doppler echocardiographic studies were performed on all patients one day before and within 24 hours after the procedure. Nine patients had an additional study 9 (3) (3–13) months later. All studies were obtained at rest. Doppler interrogation of the left ventricular outflow tract was performed from both the suprasternal and apical four chamber aortic root views. Doppler gradients were calculated by a modified Bernoulli equation ($P = 4\ v^2$).[11] In 12 patients, pulsed Doppler measurements of the maximal instantaneous pressure gradients were obtained simultaneously with catheter pressure measurements during catheterisation. The correlation coefficient between Doppler and haemodynamic (peak to peak) measurements was $r = 0{\cdot}96$ with a standard error of the estimate of 6·96. The relation between Doppler and catheter gradient was: catheter pressure gradient = 1·07 (Doppler pressure gradient) + 0·8, and used to correct the so estimated Doppler derived gradients.

We measured the left ventricular dimensions on cross sectional echocardiograms targeted by means of M mode tracings. We graded aortic incompetence according to Quinones *et al*[12]: as mild, if the diastolic back flow Doppler jet extended to the mitral valve leaflet; moderate, if the jet extended to the mid left ventricular cavity; and severe, if the jet extended to the apex during a single beat.

The study was reviewed and approved by the Human Subject Review Committee of the University of Toronto and The Hospital for Sick Children. Informed consent was obtained from all parents entering their children in the study.

STATISTICAL ANALYSIS

Data were expressed as mean (SD) and range. We used a two tailed Student's t test to compare paired data. A p value of $< 0{\cdot}05$ was regarded as significant.

TECHNIQUE OF BALLOON DILATATION

All studies were performed under general anaesthesia with either ketamine or fentanyl. Right heart catheterisation was performed in all patients and included a thermodilution determination of cardiac output. If necessary we also catheterised the left ventricle by trans atrial-septal puncture and a balloon tipped, side hole catheter (Berman angiocatheter; Critikon Inc, Tampa, Florida) placed in the left ventricle for constant monitoring during the procedure. We used a 21 gauge needle and a 6 French micropuncture sheath dilator set (Cook Inc, Bloomington, Illinois) to cannulate the femoral artery and we placed a side hole National Institute of Health (NIH) angiography catheter in the ascending aorta. Heparin sulphate (150 units/kg; maximal dose 5000 units) was given after arterial entry. We measured simultaneous arm blood pressure (by cuff) and aortic and left ventricular pressures and obtained ascending aortoangiograms of the 30° left anterior oblique and lateral projections. The position of the aortic valve was marked with a radio-opaque sticker on the chest before the angiogram and this was used as a reference throughout the procedure. We measured the diameter of the aortic valve at the hinge points from the left anterior oblique projection using the angiocatheter for magnification correction.

The retrograde NIH catheter was substituted for an end hole (Gensini angiocatheter, USCI, BARD, Inc) catheter and manoeuvred across the aortic valve over a straight guide wire. Once in position we removed the wire and replaced it with a Teflon coated exchange wire (0·035 inch, 0·889 cm; 260 cm, Cook, Inc) that curled in the ventricular apex. We removed the catheter and sheath from the femoral artery and positioned a balloon catheter 3 (12 patients) or 6 (13 patients) cm long across the outflow tract and valve over the guide wire. The balloons chosen were within 1 or 2 mm of the valve diameter as estimated from angiography.

It was always difficult to position the 3 cm length balloon across the aortic valve at full inflation and only slightly easier with the 6 cm long balloon.

Balloons of 10–20 mm in diameter were mounted on 8 or 9 French polyethylene catheter shafts (Mansfield Scientific Inc, Mansfield, Massachusetts). Once in position the balloon was inflated repeatedly (up to six times (mean 3)) until we could be certain that it was properly positioned across the valve at full inflation and the waist had disappeared. The balloon was then removed to the descending aorta while the wire was left in the ventricle. Systolic (by arm cuff) and left ventricular pressures were recorded. A second series of inflations were performed if there was no change or a change of < 20 mm Hg (four times) in the gradient or the balloon was exchanged for the next larger diameter (four patients). In one patient, with a 22 mm valve annulus, we used two 12 mm balloons; a single balloon technique was performed in the remaining patients. Inflation-deflation cycles lasted no longer than 15 seconds. Intraballoon inflation pressures were not monitored. None of the balloons ruptured.

After we removed the balloon catheter, we positioned an end hole catheter (Gensini type) high in the ascending aorta and measured simultaneous left ventricular and aortic pressures. We recorded the pressures during sinus rhythm 10–15 minutes after the end of dilatation, after the heart rate had returned to within 10% of baseline. We also measured cardiac output by thermodilution and obtained a further angiogram of the aortic root.

We calculated the aortic valve area from the Gorlin formula.[13] The degree of aortic incompetence was graded angiographically by the criteria of Hunt *et al*[14]: grade 1, a whiff of contrast was seen in the outflow tract only; grade 2, there was faint ventricular opacification with each diastole; grade 3, the ventricular chamber was outlined but contrast was less dense than in the aorta; grade 4, the left ventricle was densely opacified after three beats, and grade 5, the left ventricle became opacified within three beats.

Post-dilatation haemostasis was achieved and the leg pulse was assessed for possible thrombosis. The mean fluoroscopy times were 30 (11) (15–60) minutes and the mean duration of the catheterisations 142 (35) (85–200) minutes. All patients recovered in a post-anaesthesia area for four hours before returning to the cardiac ward.

Results

HAEMODYNAMIC DATA

Table 1 shows haemodynamic data before and immediately after balloon dilatation. Balloons ranged from 10 mm to 20 mm in diameter and were 97 (11) (69–116)% of the aortic ring diameter. The left ventricular systolic pressure was reduced by a mean of 27 (22) (0–55)% and the mean gradient across the aortic valve by 63 (21) (18–92)%. The valve area increased 96 (80) (23–270)%. Eleven patients had a gradient of <25 mm Hg after balloon dilatation, 11 between 25–50 mm Hg, and two had residual gradients of 60 and 64 mm Hg respectively. In one patient the transverse arch was tortuous and could not be transversed with a 3 cm long, 15 mm diameter balloon catheter. In two patients the pressure gradient was not reduced. In one the 3 cm long balloon was expelled from the left ventricle with each systole and could not be positioned across the aortic valve ring during inflation. In the other patient, balloon dilatation was attempted twice. In the initial attempt, the 3 cm balloon could not be stabilised in the left ventricle; at the second, three months later, we achieved an initial reduction in pressure gradient with two 6 cm long, 12 mm diameter balloons, but the cardiac index had fallen (from 2·7 to 1·7 $l/min/m^2$) and after 24 hours the left ventricular-aortic Doppler gradient was unchanged from the pre-valvotomy values.

INTERMEDIATE FOLLOW UP

Before balloon dilatation the resting Doppler gradient was 71 (18) (40–100) mm Hg, with mild aortic regurgitation in eight patients. In the first 24 hours after dilatation the Doppler gradient had fallen to 41 (16) (16–64) mm Hg ($p < 0{\cdot}001$).

After a mean 9 (3) (3–13) months follow up in nine patients, the Doppler gradient across the aortic valve was 30 (17) (10–58) mm Hg—a significant ($p < 0{\cdot}007$) reduction from the pressure gradient before dilatation. The difference between gradients immediately after dilatation and after the longer term follow up were not significant ($p < 0{\cdot}8$).

The left ventricular end diastolic dimension was on or below the 95th percentile in three and above the 95th percentile in the remaining 22 patients. In all the left ventricular posterior wall thickness was increased and in 22 the ventricular septum was hypertrophied. We found no differences in left ventricular end diastolic dimension or posterior wall and ventricular septal thicknesses immediately after dilatation.

Two patients had exercise tests after dilatation. These showed an improvement in endurance times and no ST-T wave depression, which had been present before dilatation.

COMPLICATIONS

Two patients developed transient left bundle branch block which resolved spontaneously within 24 hours. During placement of the balloon catheter occasional ventricular extrasystoles developed. During balloon inflation extrasystoles with short non-sustained runs of ventricular tachycardia were common; sinus rhythm returned when the balloon was deflated (fig 1). There were also transient ST-T changes (both depression and elevation) that reverted to a normal pattern within minutes of balloon deflation. We did not attempt to measure the rhythm or haemodynamic changes during balloon dilatation.

Vascular complications were frequent. Femoral artery occlusion manifested by an impalpable pulse occurred in 10 patients (40%) whose mean weight

Table 1 *Haemodynamic data (mean (1 SD) and range) in 25 patients before and after dilatation of the aortic valve*

Variable	*Before*	*After*	*p*
LV systolic pressure (mm Hg)	167 (32) (125–240)	128 (25) (95–190)	p < 0·001
LV end diastolic pressure (mm Hg)	12 (6) (5–30)	9 (4) (5–22)	p < 0·001
LV-AO pressure gradient (mm Hg)	66 (26) (45–114)	24 (17) (0–64)	p < 0·001
Cardiac index ($l/min^{-1}m^{-2}$)	4·3 (3) (2·4–6)	4·3 (1) (2·1–6·2)	NS
Valve area (cm^2/m^2) (10 patients)	0·53 (0·3) (0·2–1·1)	1·24 (0·2) (0·4–1·8)	p < 0·005

LV, left ventricular; LV-AO, left ventricular-aortic.

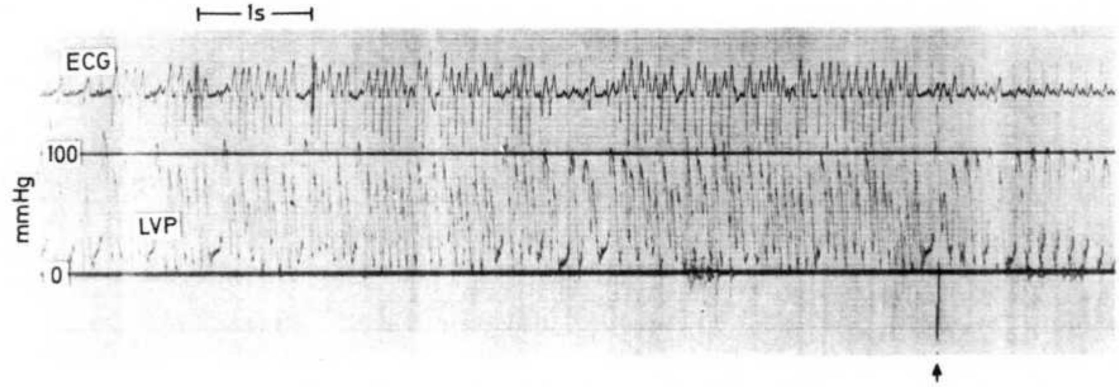

Fig 1 *Left ventricular pressure tracing and electrocardiogram during balloon inflation. The arrow indicates the end of inflation.*

was 11·4 (4) (5–20) kg. One patient recovered after a 24 hour infusion of heparin. In eight patients the femoral pulse returned after a 48–72 hour infusion of streptokinase and one patient (10 kg) needed surgical thrombectomy after an unsuccessful trial of thrombolytic treatment. Two further patients required operation—one for persistent femoral artery bleeding and one for repair of a false femoral artery aneurysm. The average hospital stay was three days in patients with an uncomplicated course and 4·3 (2) (2–8) days in those with vascular complications.

Six patients showed angiographic evidence of aortic incompetence before dilatation, and it was detected in 15 patients after dilatation. Only one patient without previous aortic incompetence and two patients with grade I aortic incompetence had severe regurgitation (grade III) after dilatation (fig 2). There were no significant differences in terms of worsening or newly acquired aortic incompetence between those patients who had a reduction of $>50\%$ in gradient and those in whom the reduction was less pronounced ($p < 0{\cdot}9$). Aortic incompetence was detected in 15 by Doppler: it was mild in nine and moderate in six. Again there was no correlation between reduction in the pressure gradient and the acquisition of or degree of aortic incompetence.

FINDINGS AT OPERATION IN PATIENTS WITH UNSUCCESSFUL BALLOON DILATATION

Four patients had an operation 6 (5) weeks (3 days to 3 months) after attempted balloon dilatation. Operations were performed at a mean age of 10·8 (4·6) (4·2–14·2) years. All patients had unsuccessful balloon dilatation, in one patient the left ventricle could not be entered and one was found to have annular and supra-annular aortic narrowing.

Two patients had open valvotomies and bicuspid valves were found. The patient with supra-annular narrowing had a tricuspid valve whose area could not be enlarged and a 21 St Jude valve was implanted. In the fourth patient a bicuspid calcified valve was found and a Kono procedure performed. This patient died soon after. Permission was not given for necropsy. No alterations in valve leaflets or commisural tears were seen in the dilated valves. The valve rings were intact and the leaflets were not damaged.

Discussion

Although the optimal treatment for the heterogenous population of patients with aortic valve stenosis under the age of six months remains controversial, surgical valvotomy under direct vision on cardiopulmonary bypass has been the standard treatment for those aged more than six months, with an early

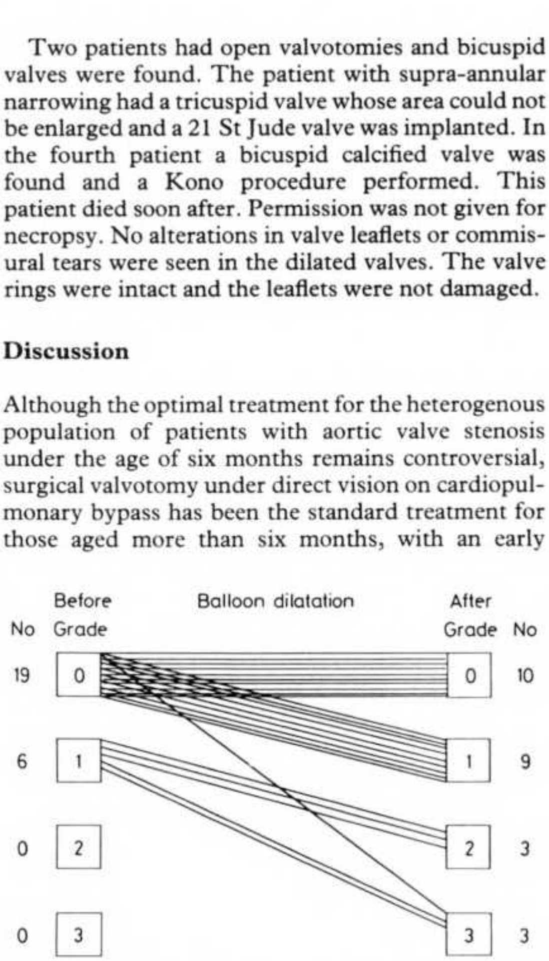

Fig 2 *Angiocardiographic assessment of aortic incompetence before and after balloon dilatation.*

Table 2 *Studies of balloon dilatation in children*

	Short term response			*Follow up (> 2 mnth)*	
Author (reference)	*No*	*% Gradient reduction (mm Hg)*	*% AI*	*No*	*Gradient (mm Hg)*
Lababidi *et al*[6], Walls *et al*[20]	27 children	62% (32 (16))	45% (new 17%)	14	37 (22)
Rupprath and Neuhaus[7]	3 (newborns)	50% (34 (6))	0%	None	
Sanchez *et al*[21]	1 (infant)	62% (40 mm Hg)	0%		30 mm Hg
Waller *et al*[22]	1 (newborn)	57% (40 mm Hg)	Died		
Helgason *et al*[8]	15 (newborns, children)	69% (28 (14))	73% (new 29%)	10	41 (25)
Choy *et al*[9]	8	49% (44 (5))	75% (new 12%)	7	No restenosis (their fig 2)

AI, aortic incompetence.

mortality of 1–2%. But surgical valvotomy is palliative.[15–19] After valvotomy patients can have residual haemodynamically important valve obstruction, aortic regurgitation, or progressive outflow obstruction that requires reoperation. In the long term most will need valve replacement. The early clinical results of percutaneous balloon dilatation of the aortic valve compare well with the results of valvotomy. Table 2 summarises the studies to date. Overall there was a 57% reduction in mean gradient in the short term. This accords with our experience (45% of our patients had a gradient of <25 mm Hg after dilatation). Short term follow up of our patients identified no restenosis detected by Doppler. These results compare favourably with the short term studies of surgical results in which the gradients after valvotomy ranged from 25 to 50 mm Hg.

There was mild to moderate aortic incompetence in 60% of patients after balloon dilatation, compared with 24% before dilatation. The overall incidence of newly acquired incompetence in three series[6,8,9] and ours, reporting a total of 71 patients, was 35%. Incompetence became worse in four of six, and was present in nine who did not have incompetence before study. The degree, however, was trivial to mild in most cases (fig 2), also reflected in other reported series. We were unable to relate the onset or degree of regurgitation to the extent of gradient reduction, although Helgason *et al* found a weak correlation.[8] In surgical valvotomy series the rate of moderate to severe postoperative incompetence varies, with a mean of 30–40%.[16,23] In this regard, follow up of this procedure has been too brief to determine if balloon induced incompetence will be progressive although logically one would not expect a different long term course. Indeed, in one surgical series, progressive insufficiency was the major reason for late reoperation.[18]

In our study arterial complications were frequent (40%); however, only three patients required surgical intervention: one each for arterial thrombosis, persistent arterial bleeding, and the development of a false aneurysm. In the others medical treatment restored arterial flow. These events appear to be more frequent in children weighing < 12 kg and seem to be related to the redundant balloon material on the catheter and the French gauge of the shaft.[24] Bundle branch block and ST-T wave depolaration abnormalities seem to be transient and well tolerated in our experience and that of others.[8,9]

TECHNICAL CONSIDERATIONS

Because of the duration of the procedure and the size and number of catheters used, we prefer to perform balloon dilatation under a general anaesthetic. We found that either a ketamine infusion or fentanyl during spontaneous ventilation was effective and safe. Neither caused complications or lengthened hospital stay.

We also prefer to have a second catheter in place in the left ventricle allowing left ventricular pressures and transvalvar gradients to be monitored before, during, and after the procedure. Because of earlier problems, we now exclusively use long balloons (5–6 cm) to ensure satisfactory positioning of the balloon across the valve during inflation. The use of the stiff guide wire (Amplatz Extra Stiff Interventional Exchange wire, 260 cm, Cook, Inc) also helps to prevent the balloon shifting position when it is inflated—others have reported this difficulty.[8] A single balloon, with a diameter that does not exceed the annulus when it is inflated was effective in animal experiments[8] and clinical series.[7,8] Aortic tears have been described when larger single balloons were used. None the less, a larger transverse diameter than the annulus can be accommodated by the pulmonary and aortic valves when two balloons are used side by side, provided that total ring circumference of the balloons is no greater than that of the undistended annulus.[25,26]

Our data indicate that balloon dilatation of the stenosed aortic valve is a safe procedure if the balloon does not exceed the annulus diameter by more than 1–2 mm. In most patients the pressure gradient can be reduced with an increase in the effective valve area, and clinically significant aortic regurgitation is uncommon, although mild incompetence develops in most. Short term follow up suggests that reduction in pressure gradient is sustained. The number of patients studied needs to be expanded but encouraging results, particularly in older children, suggest that this form of initial management is as effective as surgical valvotomy. Technical improvements and changes in the procedure may improve results and reduce complications.

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Br Heart J 1989;62:154–6

Case reports

Postpartum myocardial infarction

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SUMMARY A 29 year old woman had a myocardial infarction three weeks post partum. Coronary angiography was performed six days later. No abnormalities were seen initially, but re-injection of the left coronary artery resulted in a dissection that extended through the anterior descending and circumflex branches and a reinfarction.

This case suggests that myocardial infarctions occurring in patients with angiographically normal coronary arteries may be caused by dissections that heal by the time of catheterisation.

Myocardial infarctions are uncommon in young women, and only a small percentage occur during pregnancy, labour, or soon after delivery. The incidence is estimated at one per 10 000 deliveries,[1] and a recent review noted only 75 published reports of such cases.[2] The number of reported myocardial infarctions occurring in the early postpartum period is considerably smaller.

We report the case of a myocardial infarction occurring post partum in a 29 year old woman. We believe that this may have resulted from spontaneous dissection of the left coronary artery.

Case report

A 29 year old woman was admitted to hospital after the sudden onset of substernal pain and pressure three weeks post partum. The initial electrocardiogram showed deep ST segment depression in the inferior and precordial leads, and serum concentrations of creatine kinase rose to 2910 IU/l with 12·8% MB isotype. The ST segment depression resolved, and T wave inversion was subsequently noted in leads I, aVL, and V2–V6. The patient had no heart failure or arrhythmias, but had a brief episode of chest pain two days after admission without any increase in the titre of serum creatine kinase MB. An echocardiogram done at this time showed apical akinesis and the presence of a large apical thrombus. The patient was treated with intravenous heparin and oral diltiazem.

Coronary angiography was performed six days after the onset of chest pain. The right coronary artery was normal, and initial views of the left coronary system showed no abnormalities (fig a). After the fourth injection into the left coronary artery, however, the patient complained of chest pain. Retention of contrast agent in the left coronary artery adjacent to the ostium was noted, and a re-injection of contrast agent showed dissection of the left coronary artery extending to the proximal and middle portions of the left anterior descending artery and the proximal portion of the circumflex artery (fig b). The patient's electrocardiogram showed ST segment elevation in leads I, aVL, and V2–V6. The patient was treated with intravenous glyceryl trinitrate. On repeat re-injection, the left coronary artery and all obvious branches were seen to be patent, but the diameter of the vessel lumens appeared to be reduced, and a "double lumen" remained evident in the circumflex artery (fig c).

The patient was treated subsequently with oral diltiazem and isosorbide dinitrate. Heparin, which had been stopped before catheterisation, was not restarted. The patient's serum creatine kinase titre rose to 3817 IU/l with 23·6% MB isotype. After resolution of the pain over the next 24 hours, the

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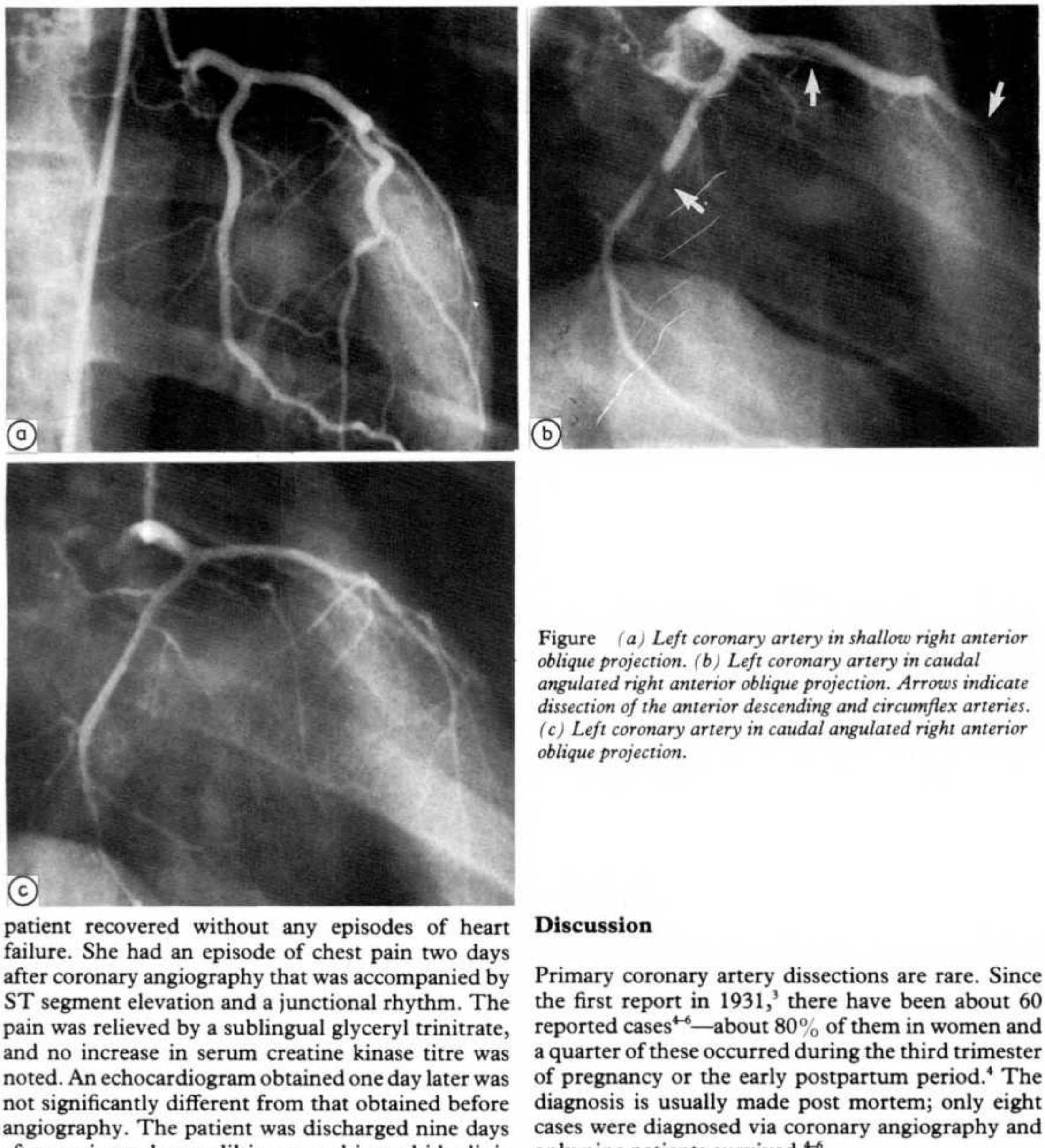

Figure *(a) Left coronary artery in shallow right anterior oblique projection. (b) Left coronary artery in caudal angulated right anterior oblique projection. Arrows indicate dissection of the anterior descending and circumflex arteries. (c) Left coronary artery in caudal angulated right anterior oblique projection.*

patient recovered without any episodes of heart failure. She had an episode of chest pain two days after coronary angiography that was accompanied by ST segment elevation and a junctional rhythm. The pain was relieved by a sublingual glyceryl trinitrate, and no increase in serum creatine kinase titre was noted. An echocardiogram obtained one day later was not significantly different from that obtained before angiography. The patient was discharged nine days after angiography on diltiazem and isosorbide dinitrate, with warfarin added two weeks later. Six months after the infarction the patient required a heart transplant for progressive heart failure. Microscopic examination confirmed the presence of a dissection in the left anterior descending artery. This was not visible on gross examination.

The patient had no history of symptoms suggestive of coronary artery disease, and no risk factors were identified. All of her pregnancies and deliveries had been normal.

Discussion

Primary coronary artery dissections are rare. Since the first report in 1931,[3] there have been about 60 reported cases[4-6]—about 80% of them in women and a quarter of these occurred during the third trimester of pregnancy or the early postpartum period.[4] The diagnosis is usually made post mortem; only eight cases were diagnosed via coronary angiography and only nine patients survived.[4-6]

The aetiology of primary coronary artery dissections is unknown. Most commonly the left coronary artery, and more specifically its anterior descending branch, is affected. Dissection typically arises within 2 cm of the left coronary ostium.[7] Haematomas are usually confined to the media without evidence of an intimal tear. Atherosclerosis of the affected vessel is generally slight or absent. Medical necrosis and infiltration of the adventitia with inflammatory cells consisting primarily of eosinophils were seen on histopathological examination.[8 9] In one case, collagen metabolism was abnormal.[10] The association of primary coronary artery dissections with peripartum and postpartum states suggests that hormonal changes and haemodynamic stresses related to pregnancy, labour, and delivery may in some way lead to a loss of structural integrity of the blood vessel wall.

We describe a myocardial infarction three weeks post partum in a 29 year old woman whose coronary arteries initially appeared normal on angiography. Most of such infarctions have been attributed by default to spasm, embolism, or thrombosis with subsequent clot lysis. In our case, however, the demonstration of dissection of the left coronary artery during catheterisation raises the possibility that the infarction five days earlier was the result of a primary coronary dissection. We cannot be certain that this was true, but we suggest that the patient's original dissection had healed incompletely, and that dye injection caused a redissection in the weakened vessel wall.

Our experience with this case has led us to suspect that many myocardial infarctions in patients with angiographically normal coronary arteries resulted from dissections that have healed by the time of angiography. There are three reports of myocardial infarctions during pregnancy in which there was no evidence of vessel obstruction at coronary angiography several months later.[11-13] In one, however, a small aneurysm was noted at the origin of the left anterior descending artery,[11] and in the remaining two cases there was tapering of the left anterior descending artery and attenuation of its branches.[12 13] These findings raise the suspicion of dissection in all of these cases. In addition, angiography may be unable to detect those coronary dissections that occur without evidence of intimal tear. In such cases, the intraluminal coronary pressure may be sufficient to maintain the patency of the affected vessel, with intramural displacement extending from the media toward the adventitia rather than the intima. A patient in whom an angiographic coronary obstruction was ascribed to atherosclerosis was found during planned bypass surgery to have an intramural haematoma in the affected vessel.[4] Evacuation of the haematoma successfully relieved the obstruction.

Our case suggests that the timing of coronary angiography after peripartum or postpartum myocardial infarctions may be crucial. We performed angiography in the early recovery period because the patient had persistent pain, diffuse ST segment changes, and no Q waves. These findings could have been the result of premature coronary atherosclerosis (possibly of the left main coronary artery), which made reinfarction likely. In this case early angiography itself resulted in a new dissection and reinfarction. One case cannot form the basis for a policy, but in view of the risk of this complication we wonder whether coronary angiography should be deferred for several weeks or months after uncomplicated peripartum and postpartum infarctions.

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Fatal intrathoracic haemorrhage after cardiopulmonary resuscitation and treatment with streptokinase and heparin

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SUMMARY A 66 year old man with acute myocardial infarction underwent cardiopulmonary resuscitation before being treated with streptokinase and heparin. Seventeen hours later he died of an intrathoracic haemorrhage caused by multiple fractures of the sternum and ribs.

Case report

A 66 year old man with no previous medical history collapsed 20 minutes after the sudden onset of retrosternal chest pain. Within ten minutes the medical team arrived and started cardiopulmonary resuscitation. The patient was intubated and defibrillated three times because of ventricular fibrillation. Adrenaline was given twice for asystole. Cardiac rhythm converted to a stable accelerated nodal rhythm and the patient was taken to hospital.

The electrocardiogram on admission showed nodal rhythm, no Q waves, and 3–5 mm ST segment elevation in leads corresponding to the inferolateral wall (I, II, III, aVF, V5, and V6). The patient was regarded as a candidate for streptokinase treatment because of the short history (two hours after onset of symptoms) and the absence of absolute contraindications. 1·5 million IU streptokinase was given over 30 minutes followed by heparin infusion (10 000 IU as a bolus injection and 15 000 IU over 24 hours).

No other agents that are associated with bleeding complications (such as antiplatelet drugs) were given to the patient.

Initially, treatment seemed to be effective. An electrocardiogram taken 6–7 hours after admission was almost normal, with no Q waves. Cardiac enzymes were measured three and 11½ hours after onset of symptoms. Total creatine kinase was 1375 and 4860 U/l, creatine kinase B 76 and 180 U/l, and aspartate aminotransferase 104 and 310 U/l respectively.

The patient became hypotensive 12½ hours after admission. Shock developed and he died 4½ hours later. The clinical diagnosis was cardiogenic shock caused by myocardial failure.

Necropsy showed a massive intrathoracic retrosternal haemorrhage. The left thoracic cavity contained 1200 ml blood and the right 600 ml. The necropsy results indicated that the source of haemorrhage was fracture of the sternum and fractures of the ribs (3rd, 4th, and 5th rib on the right side and 3rd and 4th rib on the left side) which were caused by external cardiac massage. There were no signs of cardiac or pulmonary laceration. The cause of death was hypovolaemic shock.

Discussion

Intravenous streptokinase is increasingly used to treat acute myocardial infarction. Intravenous thrombolysis is effective in 50–60% of patients,[1] but it is not without risks or side effects. Relative contraindications include recent external cardiac massage.[2 3]

To our knowledge there have been no reports of fatal haemorrhage from fractures of the sternum or ribs or both after thrombolytic treatment with streptokinase and heparin. The most severe and common haemorrhages are gastrointestinal and intracranial.[3]

External cardiac massage is estimated to cause sternal or rib fractures in 30–45% of patients.[4 5]

The rib fractures could have been solely responsible for the fatal bleeding. It seems likely, however, that the addition of streptokinase caused this massive bleeding. Heparin was also given to this patient and others have concluded that streptokinase and heparin given simultaneously may increase the risk of haemorrhage.[6]

This case highlights a risk of thrombolytic treatment in patients who have undergone cardiopulmon-

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ary resuscitation. We believe that recent external cardiac massage is a relative contraindication for thrombolytic treatment and that the benefit-risk ratio must be carefully considered in patients who have had external cardiac massage.

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Malignant melanoma of the right atrium: antemortem diagnosis by transvenous biopsy

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SUMMARY About half of all patients with malignant melanoma have cardiac metastases. Histological confirmation antemortem of a secondary malignant melanoma of the heart is difficult. The diagnosis of a secondary melanoma in the right atrium was confirmed by transvenous biopsy in a 46 year old woman who had had a melanoma excised from her right leg two years before.

Invasion of the heart by a secondary tumour is much more common than a primary cardiac neoplasm.[1] Nearly half of all patients with malignant melanomas have cardiac metastases.[2] Histological antemortem confirmation of secondary tumours of the heart is difficult and to our knowledge diagnosis of a secondary melanoma of the heart by transvenous biopsy has not been reported before. We report one such case.

Case report

A 46 year old woman was referred with influenza like symptoms and a systolic murmur. She had had a melanoma excised from her right leg two years before.

Physical examination was normal apart from a soft ejection systolic murmur at the left sternal border and a tumour plop. Full blood count, liver function tests, and electrocardiogram were normal. Chest x ray showed a small opacity in the right lower lobe. A computed tomographic scan of the thorax showed a small solitary pulmonary nodule in the right lower lobe. The right atrium was incidentally noted to be enlarged and contained several areas of low attenuation suggesting a tumour within the chamber.

Cross sectional echocardiography showed a mass in the right atrium. The exact attachments were uncertain but it seemed to be attached to the interatrial septum. The mass slightly displaced the tricuspid valve and prevented leaflet apposition in systole (figure). Colour flow Doppler showed slight tricuspid regurgitation. Right ventricular function was normal.

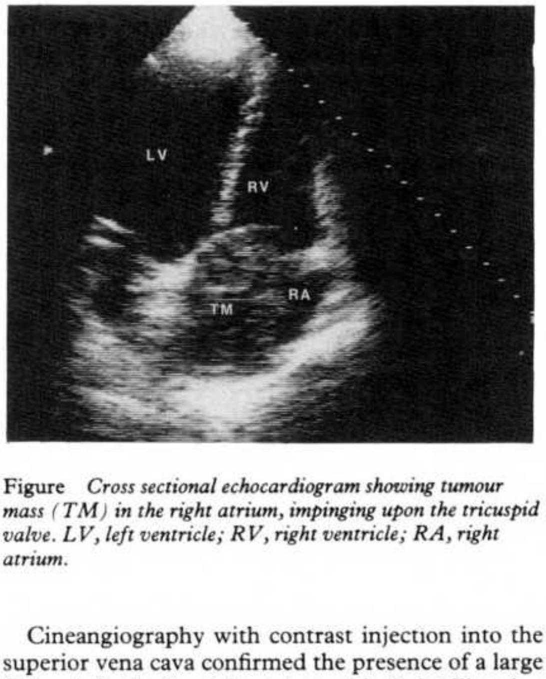

Figure *Cross sectional echocardiogram showing tumour mass (TM) in the right atrium, impinging upon the tricuspid valve. LV, left ventricle; RV, right ventricle; RA, right atrium.*

Cineangiography with contrast injection into the superior vena cava confirmed the presence of a large filling defect in the right atrium with slight dilatation of the superior vena cava. A transvenous biopsy of the right atrial mass was performed via the right internal jugular vein. Histological examination showed that the tumour was composed of a monomorphous population of polygonal cells containing large vesicular nuclei, prominent nucleoli, and abundant eosinonophilic cytoplasm. No melanin was identifiable. Immunocytochemistry showed the tumour cells to be strongly positive for S100 and vimentin, which confirmed that it was a malignant melanoma.

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Discussion

Space occupying tumours of cardiac chambers can give rise to signs and symptoms that are indistinguishable from those of other forms of myocardial or valvar heart disease.[3] Diagnosis is facilitated by a high degree of clinical suspicion. In the present case, diagnosis was established by a combination of echocardiography and cineangiography and confirmed by transvenous biopsy. This report shows that transvenous biopsy of intracavitary cardiac neoplasms is practical. However, samples may be small and histogenesis not always easily ascertained.

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Calcific stenosis of a mitral valve xenograft in a patient in chronic renal failure

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SUMMARY A 61 year old man presented with mitral regurgitation and glomerulonephritis caused by suspected infective endocarditis. His glomerulonephritis remitted on immunosuppression but mitral valve replacement with a Carpentier-Edwards porcine xenograft later proved necessary. The patient became dialysis dependent and cadaveric renal allografting was complicated by delayed graft function and refractory pulmonary oedema. Cardiac catheterisation showed severe calcification and stenosis of the xenograft with a transvalvar gradient of 23 mm Hg and despite emergency valve replacement the patient died. The valve had been in place less than five years. The rapid calcification and stenosis of a bioprosthetic heart valve calls into question the use of such prostheses in patients with chronic renal failure.

Valvar heart disease is a common complication of end stage renal failure and the lesions most commonly encountered are mitral annular calcification and aortic valve calcification.[1 2] The incidence of these lesions increases with length of time on dialysis and when there is poor control of plasma concentrations of phosphate and calcium.[2 3] They are rarely associated with haemodynamically important stenosis and they may cause tachycardia and bradycardia. We have recently encountered massive calcific excrescences on the supporting structure of a mitral valve xenograft that had been in place for less than five years in a patient with chronic renal failure. The calcification caused tight mitral stenosis but no regurgitation and resulted in a complicated clinical course after renal transplantation. Finally it caused the patient's death.

Case report

A 61 year old man was referred with oedema, episodes of severe dyspnoea, and palpitation. He had normochromic, normocytic anaemia; a pansystolic murmur compatible with mitral regurgitation; haematuria; proteinuria; and a plasma creatinine of 557 μmol/l (6·9 mg/dl). Echocardiography showed left atrial enlargement and thickened mitral cusps without visible vegetations. Despite numerous negative blood cultures a diagnosis of infective endocarditis and immune-complex mediated glomerulonephritis was made. A renal biopsy specimen showed a focal proliferative glomerulonephritis with crescent formation in 80% of glomeruli. Serum concentrations of complement were normal and the patient was treated with a combination of diuretics, antibiotics, corticosteroids, and azathioprine. His oedema subsided and his renal function improved such that his plasma creatinine fell to 250 μmol/l (2·8 mg/dl).

Dyspnoea worsened one year later and cardiac catheterisation showed severe mitral regurgitation, trivial aortic regurgitation, and normal coronary arteries. The mitral valve was replaced with a 31 mm Carpentier-Edwards porcine xenograft. The resected mitral valve had a ruptured posterior cusp and there was histological evidence of endocarditis. Although no organisms were grown from the resected material, a six week course of gentamicin and erythromycin was prescribed. The patient made an uneventful recovery and anticoagulants were stopped after three months. Renal function gradually declined, however, and the patient became dialysis dependent two years after initial presentation. Persistent hypercalcaemia associated with a high serum concentration of parathormone was noted and tertiary hyperparathyroidism was diagnosed. This resolved after total parathyroidectomy in January 1986.

In April 1986 cadaveric renal transplantation was performed and a mid-distolic murmur was heard before operation but there was no associated pansystolic murmur. After operation the renal allograft did not function immediately and the patient experien-

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ced repeated episodes of pulmonary oedema. Despite vigorous dialysis and ultrafiltration, pulmonary oedema persisted and echocardiography showed that the mitral valve prosthesis was echogenic, heavily calcific, and poorly mobile. Cardiac catheterisation confirmed severe mitral stenosis with a transvalvar gradient of 23 mm Hg but there was no evidence of regurgitation. An emergency mitral valve replacement was performed and at operation the cusps of the prosthesis were intact and there was no evidence of endocarditis. There were exuberant calcific outgrowths from the points of cusp attachment to the supporting structures, such that valve opening was severely impaired. The bioprosthesis was removed and replaced by a 29 mm Björk-Shiley tilting disc prosthesis. The postoperative course was complicated by hypotension, inotrope dependence, and an inability to wean the patient from assisted ventilation. The patient died 16 days postoperatively.

Discussion

Calcification of the mitral annulus is a common finding in the elderly at necropsy but may be present at a much earlier age in dialysis dependent patients.[2 4] It is rarely of haemodynamic importance, but mitral stenosis secondary to massive annular calcific deposits associated with a small hypertrophied left ventricle has been described.[5] The premature annular calcification in dialysis dependent patients has been associated with raised plasma concentrations of phosphate, the consequent raised calcium-phosphate product, and the length of time on dialysis.[2 3] An increased incidence of previous parathyroidectomy has also been noted.

We describe a dialysis dependent patient who was given a mitral valve xenograft because of mitral regurgitation thought to be caused by culture negative endocarditis. Prosthetic valve function seemed to be normal for over four years but a mid-diastolic murmur was heard before renal transplantation. The patient was at increased risk of dystrophic calcification because he had hyperphosphataemia caused by renal failure and hypercalcaemia caused by tertiary hyperparathyroidism while on dialysis. The diagnosis of prosthetic valve dysfunction was delayed because there was no regurgitant murmur and because it was assumed that pure stenosis was unlikely. The pattern of calcification found at operation explained the findings at auscultation in that the cusps were spared but exuberant calcification of the supporting structures prevented cusp excursion and interfered with valve opening. The consequence was a three week period of recurrent pulmonary oedema and delayed graft function caused at least in part by the low cardiac output produced by the tight stenosis.

The cause of the severe calcification of the bioprosthesis is not established but we presume that the intermittent hyperphosphataemia and the period of sustained hypercalcaemia in the year before transplantation were at least partly responsible. Early degeneration of a mitral valve bioprosthesis has previously been described in a patient taking self prescribed calcium supplementation but without documented hypercalcaemia.[6] There have also been reports of early calcification of bioprosthetic valves and early failure in children and adolescents that was ascribed to increased calcium metabolism associated with growth; and one dialysis dependent patient has been described in whom there was early failure of both mitral and aortic bioprostheses.[7]

It seems likely that the risk factors for mitral annular calcification and aortic valve calcification in dialysis dependent patients are the same for bioprosthetic xenografts in the same population.[2] Soft tissue calcification, particularly of blood vessels, is extremely common in dialysis dependent patients and because many of these patients are living longer, many are now being referred for coronary artery bypass grafts and valve replacements. The placing of bioprosthetic material in the circulation of such patients is likely to provoke dystrophic calcification and we believe that the case we describe should lead to the reconsideration of the use of bioprosthetic heart valves in dialysis dependent patients.

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Br Heart J 1989;**62**:163–4

Infective endocarditis in Crohn's disease

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From the Medical Division, Crosshouse Hospital, Kilmarnock

SUMMARY Infective endocarditis developed in a patient with Crohn's disease. This case highlights a hazard of immunosuppressive treatment in inflammatory bowel disease.

I report a case of infective endocarditis occurring as a complication of Crohn's disease. The case highlights the hazard of immunosuppressive treatment in the management of inflammatory bowel disease.

Case report

A 65 year old woman was admitted to our medical unit with a six week history of general malaise and lethargy after an episode of unexplained acute left ventricular failure that had been treated by her general practitioner at home. Myocardial infarction had been excluded by serial electrocardiograms and measurement of cardiac enzymes at that time and her general practitioner had noted an apical midsystolic murmur. Although she had responded to diuretic treatment, she continued to feel unwell with a loss of appetite and concomitant weight loss of 12 kg over this period. She had had Crohn's disease that predominantly affected the large bowel diagnosed three years before and had initially responded poorly to prednisolone and mesalazine. She had subsequently required azathioprine in addition to steroids to control her bowel symptoms. Apart from a recent exacerbation preceding her current illness, Crohn's disease had otherwise remained quiescent. She had not had sigmoidoscopy or any other investigations of her large bowel for more than eight months. There was no history of rheumatic fever or valvar heart disease.

At admission she looked generally well and was not dyspnoeic at rest. She was moderately obese and there was mild finger clubbing. No splinter haemorrhages were evident and she was not feverish. She had sinus tachycardia of 120 beats/minute, blood pressure of 160/90 mm Hg, an apical and basal midsystolic murmur, and an early diastolic murmur localised to the left sternal edge. There was no clinical or radiological evidence of left ventricular failure. A combined M mode and cross sectional echocardiogram showed a normal mitral valve with mild left atrial dilatation. Large vegetations were identified on the aortic valve (figs 1 and 2), and aortic incompetence was easily confirmed on Doppler echocardiography. All six blood cultures grew *Streptococcus faecalis*.

She was treated with intravenous benzylpenicillin (3 megaunits four times daily) and gentamicin (80 mg twice daily) and transferred to the regional cardiothoracic centre at the Western Infirmary, Glasgow for further assessment. She initially appeared stable but subsequently recurrent pyrexia developed with

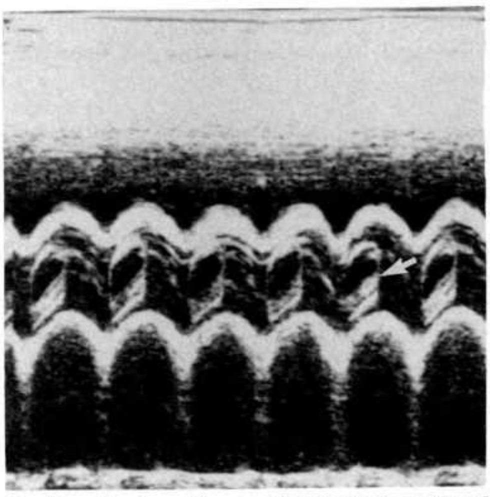

Fig 1 *M mode echocardiogram of the patient's aortic valve. The vegetation (arrow) was best shown during systole as an echo producing mass attached to the non-coronary cusp that did not restrict valve motion.*

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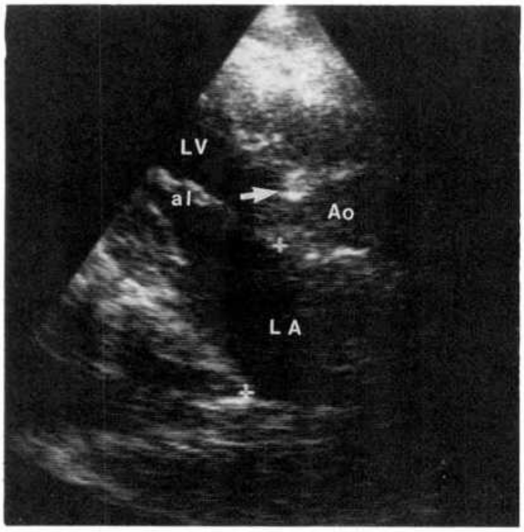

Fig 2 *Cross sectional echocardiogram of the patient in the long axis left parasternal view. Vegetation (arrow) was attached to the right coronary cusp. Ao, aorta; LA, left atrium; al, anterior mitral valve leaflet; LV, left ventricle.*

further rises in her C reactive protein. Diuretics did not control her cardiac failure and she required emergency aortic valve replacement. Her aortic valve was found to be covered with large vegetations resulting in a mixture of stenosis and incompetence. Cultures of the vegetations were sterile. Her postoperative progress was satisfactory and she remains well six months later despite a further admission with a relapse of Crohn's disease when steroid treatment was inadvertently stopped. Her bowel symptoms resolved when treatment with prednisolone was restarted and there was no evidence of recurrence of infection.

Discussion

Immunosuppression increases the risk of infective endocarditis.[1-3] Infection, particularly when the causal organisms include *Streptococcus faecalis* and *Streptococcus bovis,* may also complicate gastroenterological disorders.[4] So far these have been reported in patients with liver disease, gall bladder disease, diverticulitis, and colorectal carcinoma,[1 2] but not in patients with Crohn's disease.

It is likely that the exacerbation of Crohn's disease in this case led to a constant bacteraemia which resulted in infection of the aortic valve, possibly as a direct sequel of suppression of the patient's native immune response by prednisolone and azathioprine. None the less, the risk of infective endocarditis in such circumstances must be small because immunosuppressive treatment is regularly used to treat chronic inflammatory bowel disease.

I thank Dr J Morrow, consultant gastroenterologist, for permission to report this case.

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Notices

British Cardiac Society

The Annual General Meeting will take place in Torquay on 22 to 25 May 1990.

Comparative electrocardiology

A workshop on Comparative Electrocardiology will be held in Amsterdam on 12 and 13 October 1989. Inquiries to Dr Frits L Meijler, Interuniversity Cardiology Institute of The Netherlands, PO Box 19258, 3501 DG Utrecht, The Netherlands.

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Br Heart J 1989;62:165–70

Cardiac parasympathetic activity during the early hours of acute myocardial infarction

D McAREAVEY, J M M NEILSON, D J EWING, D C RUSSELL

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SUMMARY Cardiac parasympathetic activity was assessed in 21 patients during the first 24 hours of acute myocardial infarction by measuring abrupt beat by beat changes in RR interval, which are expressed as "RR counts". Eleven patients had inferior wall infarction and 10 had anterior wall myocardial infarction. The whole recording period was analysed in 11 patients (five inferior and six anterior), and intermittent hourly periods were analysed in all 21 subjects. Mean RR counts were significantly lower in patients with anterior than inferior infarction, and below the normal range. Although mean heart rates were faster in the group with anterior infarction, there was a dissociation between RR counts and mean heart rate that was consistent with RR interval variability being an independent measure of parasympathetic activity.

This study indicates that cardiac parasympathetic activity during acute myocardial infarction can be simply and reliably assessed from continuous electrocardiographic recordings, and it showed significantly lower cardiac parasympathetic activity in patients with anterior infarction.

Autonomic disturbances may be detected early after acute myocardial infarction in man.[1] These vary from patient to patient with either apparent sympathetic or parasympathetic effects predominating at any one time, or both occurring concurrently, particularly during the first few hours.[2] The balance of autonomic activity during this period may be important in determining the extent of subsequent myocardial ischaemic injury[3] and the vulnerability to ventricular fibrillation.[4] In general, patients with inferior myocardial infarction more commonly develop bradycardia and transient hypotension, while those with anterior myocardial infarction may develop a faster heart rate.

Measurement of sympathetic and parasympathetic activity in man after a myocardial infarction poses some difficulties. Heart rate changes alone are insufficiently precise because they reflect not only the overall balance of autonomic activity but also hormonal and other influences. Pharmacological intervention studies are not practicable because the drugs given may alter other reflex responses and make interpretation difficult. Other possible techniques are either invasive or cumbersome.[5]

Recently we described a method for measuring cardiac parasympathetic activity continuously from ambulatory electrocardiographic recordings by analysing abrupt beat by beat changes in RR interval.[6] The aim of the present study was to apply this technique to the assessment of cardiac parasympathetic activity during the early hours of acute myocardial infarction. We studied patients with acute inferior and acute anterior wall myocardial infarction for up to 24 hours after the onset of chest pain.

Patients and methods

PATIENTS

We studied 21 patients (16 men and five women, aged 38–69 years) who were admitted to hospital within the first few hours of onset of symptoms of acute myocardial infarction (table 1). The diagnosis of acute myocardial infarction was confirmed by the electrocardiographic changes of Q wave infarction and standard serum creatine kinase activity above the normal range for our laboratory. No patient with a history of diabetes, previous treatment with a β adrenoceptor blocking drug or hypotensive agent, or known previous myocardial infarction was included. Eleven patients had electrocardiographic evidence of inferior wall infarction (inferior group) and 10 of anterior wall infarction (anterior group).

Reprints will not be available from the authors.

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Table 1 *Clinical details of patients with acute myocardial infarction (mean (SEM or range))*

Site of infarction	*Inferior*	*Anterior*
Number	11	10
Age (yr)	56·7 (38–69)	59·5 (51–65)
Peak creatine kinase (units/l)	1748 (213)	2116 (364)
Systolic blood pressure (mm Hg)	137 (10)	140 (9)
Diastolic blood pressure (mm Hg)	86 (6)	88 (5)
Time of admission after onset of symptoms (h)	4·5 (3–6)	4·8 (3–9)
Number of admissions between:		
0800–1959 h	7	5
2000–0759 h	4	5

Their results were compared with 24 hour electrocardiographic tape recordings from 58 normal ambulant men aged 18–65 years who had no known disease and were not taking regular medications. Twenty four hour electrocardiographic tapes were also recorded from six young men aged 18–27 years who were confined to bed after trauma with leg or pelvic fractures. The tapes were recorded several days after operation when they were fully conscious.

ELECTROCARDIOGRAPHIC RECORDING

Electrocardiographic signals were recorded on magnetic tape from routine precordial monitoring electrodes from admission until 24 hours after the onset of pain. A digital recording clock provided a time track on a second channel of the tape recorder. The times of clinical events such as recurrence of chest pain, drug administration, and patient activities were recorded at the bedside.

ANALYSIS OF VARIATION IN RR INTERVAL

Continuous assessment

The 24 hour electrocardiographic tapes were analysed for the presence of ventricular extrasystoles by a pathfinder arrhythmia analyser (Reynolds Medical). Ten patients with more than five extrasystole beats per hour were excluded from this part of the study. Recordings from the remaining patients (five patients from the inferior group and six patients from the anterior group (all men)) were then analysed as previously described.[6] We counted the number of times successive RR intervals differed by more than 50 ms from the preceding RR interval. The electrocardiographic signals were played at 60 times real speed into a QRS wave detector[7] which generated timing pulses. These were passed to a specially designed microcomputer which measured each RR interval. Hourly counts of mean RR interval and RR interval differences in excess of 50 ms were derived and have been called "RR counts (C)". For the purpose of this analysis only those counts where the RR interval lengthened were used, because previous work has indicated that there are no significant differences between numbers of lengthened and shortened RR counts.[6] The computer was programmed to exclude changes in RR interval that exceeded 300 ms to avoid false counts caused by missed beats and most ectopic complexes. A running oscilloscopic trend plot of successive RR intervals and a display of the electrocardiographic signal being processed allowed the operator to monitor signal quality, adjust trigger threshold to optimise the rejection of noise and artefact, and to identify arrhythmic episodes.

Intermittent assessment

To obtain information on the patients excluded from the continuous assessment because of ectopic activity, additional analyses of intermittent short periods were performed in all 21 subjects. This was done by replaying QRS trigger pulses through a BBC B microprocessor programmed to measure successive RR intervals. Sampling periods of 400 beats were selected every hour from the tape recorded electrocardiographic signals, avoiding periods with considerable numbers of extrasystoles. Trend plots of RR intervals and beat by beat RR interval differences were displayed for each sampling period (fig 1). Coupling intervals and compensatory pauses associated with extrasystoles were identified by comparison with a simultaneously recorded electrocardiogram and excluded from further analysis. A score of "RR counts (I)" was derived by calculating the number of times within the 400 beat sequence that successive RR interval differences exceeded 50 ms during sinus rhythm. In those patients in whom, because of extrasystoles, less than 400 sinus beats were used to measure "RR counts (I)", the results were expressed as a proportion of 400 beats. The mean (SD) number of sinus beats used in these patients was 379 (27).

STATISTICAL ANALYSIS

Statistical comparisons between groups were performed by a Wilcoxon rank sum test. A Wilcoxon signed rank test was used to test for significant trends.

Results

CLINICAL PRESENTATION

There were no significant differences detected between patients with inferior and anterior wall myocardial infarction in age, sex, arterial blood pressure eight hours after onset of symptoms, or peak activity of serum creatine kinase (table 1). All patients received opiates either before or on admission to hospital. Additional opiates were adminis-

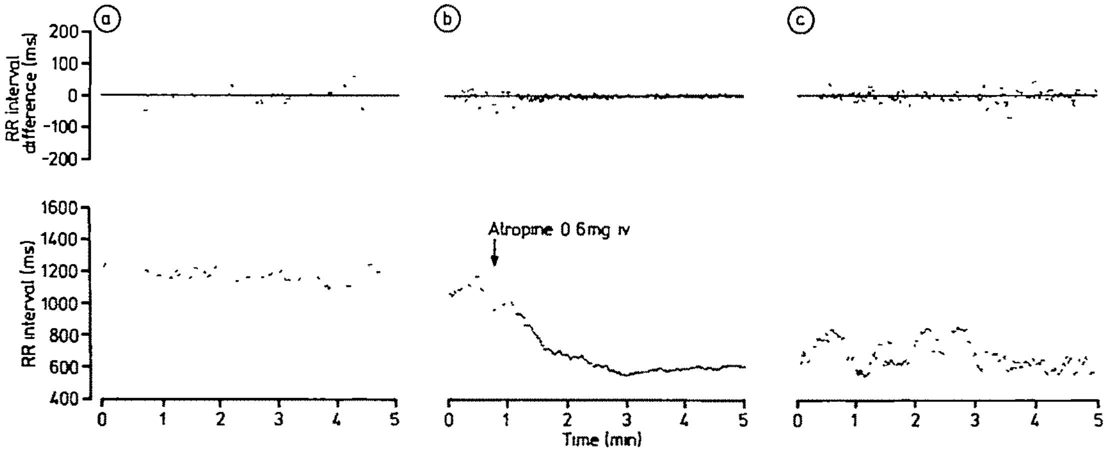

Fig 1 *Individual RR interval differences and RR intervals in a patient (a) before, (b) during, and (c) 90 minutes after 0 6 mg intravenous atropine.*

tered to 10 patients (five with inferior and five with anterior infarction) for recurrence of chest pain. There were no clear patterns in timing of chest pain or opiate administration, although statistical analysis was not possible. Five patients (three inferior and two anterior infarcts) were treated with intravenous diuretics. Symptoms and signs possibly attributable to vagal activity such as nausea, vomiting, and bradycardias, were commoner in patients with inferior myocardial infarction ($n = 7$); than in those with anterior myocardial infarction ($n = 2$); and those that could be attributable to increased sympathetic activity, such as sweating and peripheral vasoconstriction, occurred in two of the patients with anterior infarction.

ANALYSIS OF VARIATION IN RR INTERVAL

RR interval

Table 2 shows the results of RR interval analysis. Patients with anterior myocardial infarction had shorter mean RR intervals (faster heart rates) than patients with inferior infarction on both continuous and intermittent assessments over the recording period. In the smaller number of patients with continuous assessment mean RR intervals did not change significantly in either the inferior or anterior groups between the early (4–9 hours) and late (19–24 hours) periods of recording. In the larger number of patients who had intermittent analysis the mean RR interval lengthened significantly ($p < 0{\cdot}01$) in the inferior group towards the end of the 24 hour period.

RR INTERVAL VARIATION ("COUNTS") (TABLE 2 AND FIGS 2, 3, AND 4)

The groups with anterior myocardial infarction had significantly lower RR counts (C) and RR counts (I) than the group with inferior infarction throughout the 24 hour recording period ($p < 0{\cdot}02$). RR counts (C) were not significantly different in either group when early and late counts were compared. The RR

Table 2 *Group mean counts and RR intervals for the continuous and intermittent analyses in patients with inferior myocardial infarction or anterior myocardial infarction (mean (SD))*

	RR interval variation			*Mean RR interval (ms)*		
	Over whole 4–24 h period	*Early (4–9 h)*	*Late (19–24 h)*	*Over whole 4–24 h period*	*Early (4–9 h)*	*Late (19–24 h)*
Intermittent analysis: RR counts (I) (mean counts/400 beats)						
Inferior (n = 11)	15 (2)	11 (16)	20 (24)	854 (135)	787 (132)	891 (673)
Anterior (n = 10)	3 (5)	2 (2)	3 (6)	682 (130)	687 (89)	673 (135)
Difference	$p < 0{\cdot}02$	NS	$p < 0{\cdot}05$	$p < 0{\cdot}01$	NS	$p < 0{\cdot}01$
Continuous analysis: RR counts (C) (mean hourly counts)						
Inferior (n = 5)	69 (39)	60 (52)	71 (47)	866 (169)	839 (188)	867 (166)
Anterior (n = 6)	12 (9)	17 (19)	11 (8)	630 (92)	670 (78)	616 (94)
Difference	$p < 0{\cdot}01$	NS	$p < 0{\cdot}01$	$p < 0{\cdot}02$	NS	$p < 0{\cdot}01$

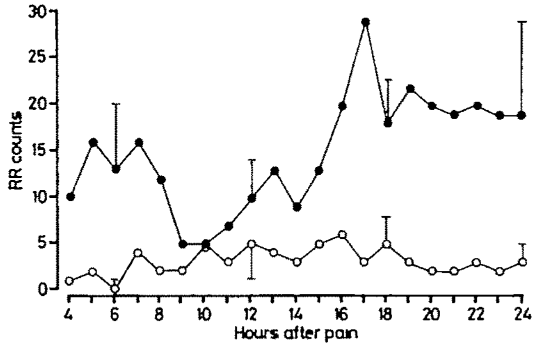

Fig 2 Variation in RR interval (group mean RR counts (I)/400 beats) during the 24 h after the onset of symptoms in patients with inferior (●——●, n = 11), and anterior (○——○, n = 10) myocardial infarction. Bars are SEM.

counts (I) in fig 2 show that with anterior infarction counts are low throughout, whereas with inferior infarction counts are higher and significantly so at most points during the 24 hour recording period. Figure 3 shows the value for RR counts (C) obtained in 58 ambulant men, together with counts for six young men who were in bed recovering from trauma but who were otherwise normal. When RR counts (C) in the myocardial infarction patients were compared with these normal values (fig 4), those with inferior myocardial infarction fell within the normal range whereas those with anterior myocardial infarction had reduced counts.

Effect of atropine

The abrupt variation in RR interval was probably mediated by the vagus nerve. This is suggested by its disappearance after intravenous atropine. Figure 1 shows the effect of atropine in a patient with acute inferior myocardial infarction. Before atropine, the RR interval was around 1200 ms and there was considerable RR interval variation. After 0·6 mg intravenous atropine the mean RR interval shortened to 600 ms and RR interval variation was abolished. One and a half hours later there was again considerable RR interval variation although the mean RR interval itself remained unchanged at 600 ms.

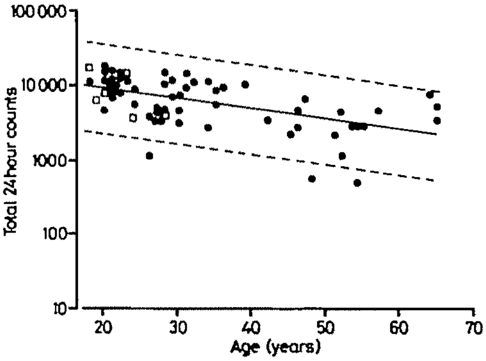

Fig 3 Individual total 24 hour RR counts (C) in 58 healthy ambulant men (●), and six healthy young men confined to bed with fractures (□). Dotted lines represent the age related 95% confidence interval for men, derived from the counts of the 58 healthy men.

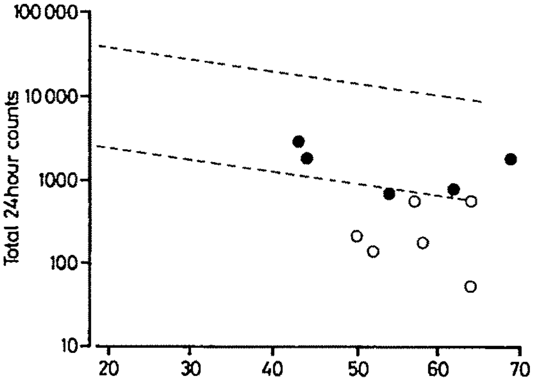

Fig 4 Individual total 24 hour RR counts (C) in five men with inferior (●) and six men with anterior (○) myocardial infarction. The dotted lines represent the age related 95% tolerance limits for men.

Discussion

We studied the technique of non-invasive assessment of cardiac parasympathetic activity from abrupt beat by beat RR interval changes during the early hours of acute myocardial infarction. Such RR interval changes were less frequent in patients with anterior than inferior myocardial infarction independent of underlying heart rate. Individual RR interval patterns were, however, variable from patient to patient. In some, the RR interval changed irregularly throughout the period of recording; in others, the trace of RR interval was smooth and regular for prolonged periods, suggesting consistently low or absent cardiac efferent vagal activity throughout the period of recording; in yet others, regular and irregular periods were present at variable times.

Previous work in humans has shown that abrupt changes in RR interval such as those occurring at the start of muscular exercise, standing up and lying down, are mediated by the vagus nerve.[8 9] Variation in RR interval is abolished in animals by cutting the vagus nerve,[10] and also in man by giving atropine but is unaffected by β adrenoceptor blockade.[11 12] Patients with transplanted hearts and diabetic patients with evidence from the cardiovascular reflex of vagal damage have almost no variation in RR interval.[6] In addition, animal studies suggest that the degree of respiratory sinus arrhythmia is directly related to vagal efferent traffic.[13-15] Thus we feel that RR interval variation, as assessed by our method of measuring RR interval differences, provides a useful index of cardiac parasympathetic activity, which can be recorded and measured over prolonged periods. The parasympathetic mediation of variation in RR interval is further suggested by our observations with atropine. The return of variation in RR interval in our patient with myocardial infarction 90 minutes after he was given atropine was not accompanied by a slowing in heart rate, which suggests that control of variation in heart rate might be mediated separately from that of prevailing heart rate. While the exact relation between prevailing heart rate and heart rate variation is complex, we have previously shown in healthy people and diabetic patients that variation in heart rate does not parallel prevailing heart rate and that some people with high heart rates also had high heart rate variation.[6]

No obvious factors seemed to determine the episodic and irregular timing of these presumed parasympathetically mediated changes. They probably reflect changes in automonic reflex responses, which are influenced by numerous factors including central stimuli and multiple cardiac, respiratory, and baroreceptor afferent stimuli.[16] Asynchrony of vagal afferent and sinoatrial nodal pacemaker activity may also contribute.[17] Responses may be further modulated by intracardiac sympathetic-parasympathetic interactions involving nerve terminals, postsynaptic, and cellular mechanisms[18 19] and sino-atrial chromaffin cells.[17]

The lower counts in our patients with anterior infarction cannot be attributed to bed rest alone because healthy people confined to bed for other reasons had counts within our expected range for healthy ambulant people (fig 3). Furthermore, in so far as can be judged from this small series, differences in counts were not accounted for by diurnal change, the drugs administered, or clinical features. A possible mechanism for reduced variation in RR interval during anterior infarction is the higher density of parasympathetic innervation to the posterior and inferior left ventricular walls[20] and known preponderance of parasympathetically mediated reflex activity during ischaemia or infarction of these regions.[21] Such dependence of autonomic responses upon site of infarction was shown experimentally after acute coronary occlusions in the cat or dog.[21 22] Differential responses atrributable to the preferential location of vagal afferents in the inferior and posteroinferior regions of the left ventricular wall can mediate depressor reflexes during the periods of acute ischaemic injury very similar to those seen in humans. Associated infarction of the right ventricle, which may accompany acute infarction of the inferior left ventricular wall, can stimulate right atrial and ventricular cardiac receptors and initiate a vagally mediated cardioinhibitory Bezold-Jarisch reflex.[16 18 19] An alternative possibility is that differences in "counts" between patients with anterior and inferior infarction may result from enhanced vagal responses after ischaemia of the sinoatrial node associated with occlusion of the right coronary artery.[23]

In conclusion, this study showed that differing degrees of cardiac parasympathetic activity can occur in individual patients during the first 24 hours after onset of symptoms of acute myocardial infarction that may not be manifest by heart rate changes alone, with significantly lower activity in anterior infarction than in inferior infarction. These observations raise the possibility of predicting neurogenically triggered serious cardiac arrhythmias. Transient autonomic imbalances are associated with enhanced electrical instability of the heart[24] and there is evidence to suggest that transient changes in parasympathetic activity may precede episodes of ventricular fibrillation.[25] Assessment of heart rate variability may also be of prognostic value in the months after acute myocardial infarction.[26]

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Aortic regurgitation associated with hypertrophic cardiomyopathy: a colour Doppler echocardiographic study

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SUMMARY The frequency, severity, and cause of aortic regurgitation were assessed by colour Doppler and cross sectional echocardiography in 87 patients (mean (SD) age 57 (12) years) with hypertrophic cardiomyopathy, and 48 age matched controls (57 (8) years). Aortic regurgitant murmurs were recorded in only three of 87 patients and in none of the controls. Colour Doppler echocardiography showed an aortic regurgitant signal in 20 (23%) of the patients and three (6%) of the 48 controls. The colour Doppler signals typical of aortic regurgitation were limited to the left ventricular outflow tract. There were no significant differences between patients with hypertrophic cardiomyopathy with and without aortic regurgitation in terms of age (59 years *v* 56 years), blood pressure (140/84 mm Hg *v* 136/80 mm Hg), aortic diameter (34 mm *v* 33 mm), or frequency of calcification of the aortic valve (15% *v* 10%) and of systolic anterior motion of the mitral valve with mitral-septal contact (25% *v* 16%). On cross sectional echocardiograms, the degree of septal protrusion into the left ventricular outflow tract during systole was significantly more prominent (15 *v* 10 mm), and the portion of the basal septum that protruded most deeply into the left ventricular outflow tract was significantly closer to the aortic annulus in patients with aortic regurgitation than in those without it (11 *v* 14 mm).

Mild aortic regurgitation was found in almost a quarter of patients with hypertrophic cardiomyopathy. The regurgitation was related to the morphological abnormality of the left ventricular outflow tract.

In hypertrophic cardiomyopathy, aortic regurgitation has long been thought to be rare. Before the era of echocardiography, only a few reports reported such as association[1 2] and we had treated only one patient with both conditions. In this patient an aortic regurgitant murmur developed gradually. Even now that echocardiography is widely used there are still a few reports of such cases[3 4] and even fewer reports of the incidence and cause of aortic regurgitation in patients with hypertrophic cardiomyopathy.[5] We assessed the frequency, severity, and cause of aortic regurgitation in patients with hypertrophic cardiomyopathy by cross sectional and colour Doppler echocardiography.

Patients and methods

SELECTION OF PATIENTS

We evaluated 91 consecutive patients with hypertrophic cardiomyopathy in the Second Department of Internal Medicine, University of Tokyo, between January 1985 and May 1987. The diagnosis of hypertrophic cardiomyopathy was made in each patient by the echocardiographic visualisation of a non-dilated hypertrophic left ventricle and asymmetrical septal hypertrophy without any other known causes of hypertrophy.[6] In all 91 patients, the interventricular septal thickness was more than 15 mm and the ratio of the septal thickness to the posterior wall thickness in diastole was greater than 1·3. One patient with symmetrical hypertrophy and one patient with apical hypertrophy were not included in the study group because of this diagnostic criteria. Four patients with apical hypertrophy,

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however, were included in the series because they had additional septal hypertrophy. Of 91 patients, two elderly women and two middle aged men were excluded because of inadequate colour flow patterns. We report on the remaining 87 patients with hypertrophic cardiomyopathy (63 men and 24 women, mean age 57 (12) years and 48 age matched controls (32 men and 16 women (57 (8) years)). None of the controls had a history of cardiac disease or systemic hypertension or were on medication at the time of study. They all had a normal 12 lead electrocardiogram, normal chest *x* ray films, and normal physical findings.

PHONOCARDIOGRAPHY

Careful auscultation was performed to detect an aortic regurgitant murmur in each subject before the phonocardiographic examination. The auscultatory findings were confirmed by recording a high-pitched diastolic murmur at the point of maximum intensity with a high quality multichannel phonocardiograph or Siemens Mingograph 82.

COLOUR DOPPLER ECHOCARDIOGRAPHY

Colour Doppler, cross sectional, and M mode echocardiographic examinations were performed with Aloka SSD 880, 860, or 870 with 2·5 or 3·5 MHz transducers. Subjects were routinely studied in the left lateral position. The aortic regurgitant jet was sought on multiple planes in each subject, including parasternal long axis and short axis and apical long axis four chamber views. In each view, the transducer was carefully oriented to show maximally the regurgitant jets. Aortic regurgitation was considered to be present when an abnormal diastolic flow originating from the aortic valve was visualised in the left ventricle. Diastolic flow was identified as abnormal either because there was flow in an abnormal direction (that is, away from the aortic valve during diastole) or because of a mosaic pattern indicating turbulent flow.

CROSS SECTIONAL ECHOCARDIOGRAPHY

On cross sectional echocardiograms, calcification of the aortic valves and systolic anterior motion of the mitral valve with mitral-septal contact were sought on multiple planes.

MEASUREMENTS OF D$_1$ AND D$_2$ (fig 1)

On the parasternal long axis view in systole, a line connecting the two points of the origin of the aortic valve was used to locate the plane of the aortic annulus (A–A′). From the point of right coronary cusp origin (A), a line (B) was drawn along the aortic long axis which was vertical to the line of the aortic annulus (A–A′). The distance (D$_1$) from the point of the interventricular septum that protruded most deeply into the left ventricular outflow tract (C) to the line B was measured. The distance (D$_2$) from the point C to the aortic annulus line (A–A′) was also measured. Then D$_1$ was calculated as a percentage of D$_2$.

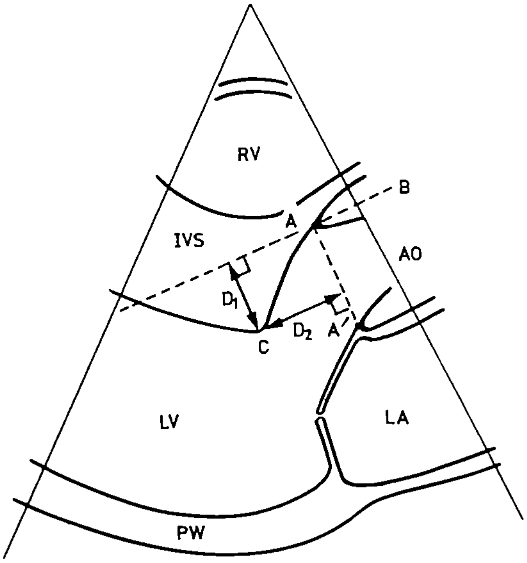

Fig 1 *Measurements of D$_1$ and D$_2$. On the parasternal long axis view in systole, a line connecting the two points of the origin of the aortic valve was used to locate the plane of the aortic annulus (A–A′). From the point of right coronary cusp origin (A), a line (B) was drawn along the aortic long axis which was vertical to the aortic annulus (A–A′). The distance (D$_1$) from the point at which the interventricular septum protruded most deeply into the left ventricular outflow tract (C) to the line B was measured, as was the distance (D$_2$) from the point C to the aortic annulus line (A–A′). AO, aorta; IVS, interventricular septum; LA, left atrium, LV, left ventricle; PW, left ventricular posterior wall; RV, right ventricle.*

M MODE ECHOCARDIOGRAPHY

Standard M mode echocardiograms were recorded from the parasternal window on a strip chart at a paper speed of 50 or 100 mm/s according to the recommendations of the American Society of Echocardiography.[7] The following were measured: left ventricular end diastolic dimension, left ventricular end systolic dimension, end diastolic left ventricular posterior wall thickness, end diastolic interventricular septal thickness, aortic root diameter, and left atrial dimension. The ratio of end diastolic interventricular septal thickness to end diastolic left ventricular posterior wall thickness was calculated.

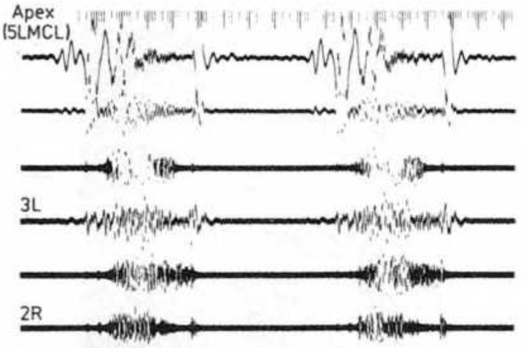

Fig 2 *Phonocardiograms of a patient with hypertrophic cardiomyopathy. An aortic regurgitant murmur was not detected at the age of 15 (upper panel), while high-pitched diastolic murmur was recorded at the fourth left intercostal space at the age of 30 (lower panel).*

Blood pressure was measured at the time of the study by the standard cuff method with an appropriately sized cuff.

STATISTICAL ANALYSIS

Data were expressed as mean (SD). Group data were compared by Student's t test or a χ^2 test. Variability was expressed as the percentage error of each measurement and was determined as the difference between the two observations divided by the mean value of the two observations. A probability (p) value of $< 0{\cdot}05$ was regarded as statistically significant.

Results

AN ILLUSTRATIVE CASE

A 15 year old boy with hypertrophic obstructive cardiomyopathy was referred to our department in 1971 because of an illness discovered in 1964. He had a loud systolic ejection murmur with late peak intensity and fourth heart sound and no diastolic regurgitant murmur in the initial phonocardiogram (fig 2, upper panel). A high pitched diastolic murmur gradually appeared during the next 10 years. Phonocardiography showed the diastolic murmur in 1986 (fig 2, lower panel). An aortic regurgitant signal was recognised by colour Doppler echocardiography (fig 3).

FREQUENCY OF AORTIC REGURGITATION IN PATIENTS WITH HYPERTROPHIC CARDIOMYOPATHY AND IN CONTROLS

An aortic regurgitant murmur was heard or recorded in only three (3%) of 87 patients with hypertrophic cardiomyopathy and in none in the controls. Colour Doppler echocardiography showed aortic regurgitant signals in 20 (23%) of 87 patients with hypertrophic cardiomyopathy and in three (6%) of the 48 controls. The colour Doppler signals of aortic regurgitation were restricted to the left ventricular outflow tract in patients with hypertrophic cardiomyopathy and the controls.

COMPARISON OF PATIENTS WITH HYPERTROPHIC CARDIOMYOPATHY WITH AORTIC REGURGITATION AND WITHOUT (table)

There were no statistically significant differences

Table *Comparison of clinical and echocardiographic data in patients with hypertrophic cardiomyopathy with aortic regurgitation and without*

	HCM with AR		*HCM without AR*		*p value*
n	20		67		NS
Age (yr)	59	(13)	56	(13)	NS
sBP (mm Hg)	140	(22)	136	(24)	NS
dBP (mm Hg)	84	(19)	80	(14)	NS
AOD (mm)	34	(5·2)	33	(3·6)	NS
LAD (mm)	42	(6·3)	43	(6·0)	NS
LVDs (mm)	29	(6·4)	26	(5·7)	NS
LVDd (mm)	46	(6·0)	44	(5·2)	NS
IVS (mm)	21	(5·0)	21	(5·3)	NS
LVPW (mm)	13	(3·0)	12	(2·2)	NS
IVS/LVPW	1·6	(0·2)	1·7	(0·4)	NS
Cal of AV	3/20	(15%)	7/68	(10%)	NS
SAM	5/20	(25%)	11/68	(16%)	NS
D_1 (mm)	15	(5·0)	10	(3·7)	<0·001
D_2 (mm)	11	(6·1)	14	(3·9)	<0·001
D_1/D_2 (%)	165	(72)	74	(31)	<0·001

AR, aortic regurgitation; AOD, aortic root diameter; Cal of AV, calcification of the aortic valve; dBP, diastolic blood pressure; LAD, maximum left atrial size; LVDd, end diastolic left ventricular dimension; LVDs, end systolic left ventricular dimension; LVPW, end diastolic left ventricular posterior wall thickness; HCM, hypertrophic cardiomyopathy; IVS, end diastolic ventricular septal thickness; SAM, systolic anterior motion of the mitral valve with mitral-septal contact; sBP, systolic blood pressure; D_1 and D_2 are defined in fig 1.

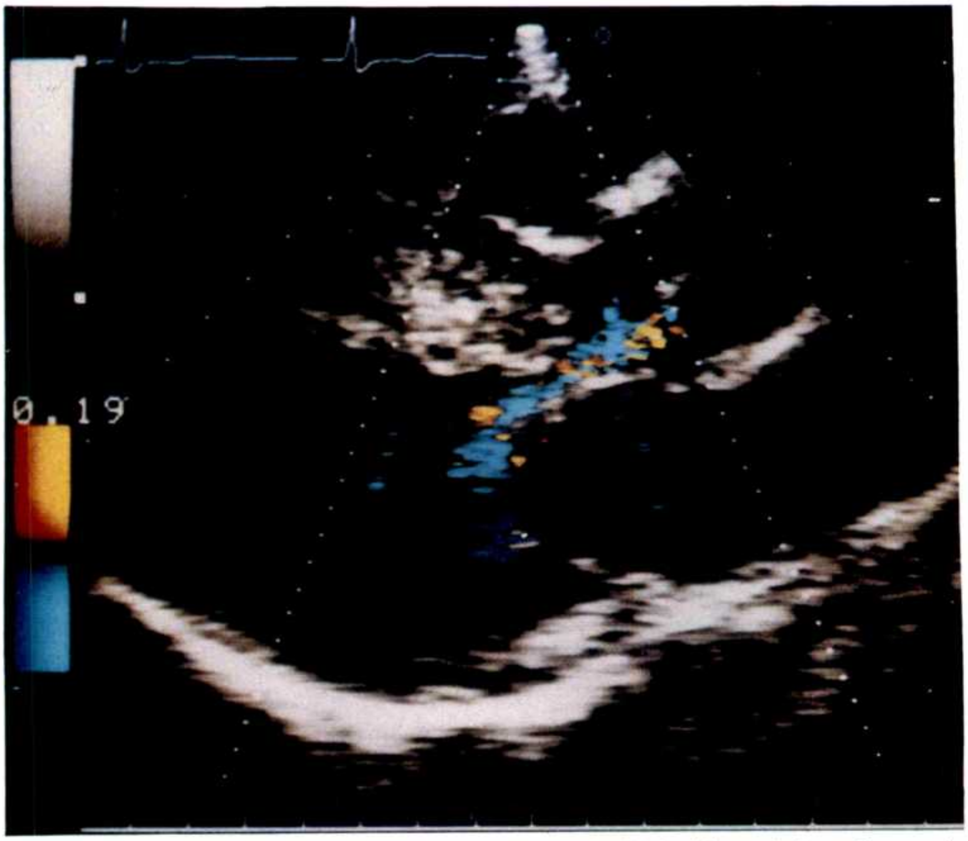

Fig 3 *Colour Doppler echocardiogram showing aortic regurgitant signal in the left ventricular outflow tract in the same patient as fig 2.*

between most variables in patients with hypertrophic cardiomyopathy who had aortic regurgitation and those who did not. These were age, blood pressure, left ventricular end diastolic dimension, left ventricular end systolic dimension, end diastolic left ventricular posterior wall thickness, end diastolic interventricular septal thickness, the ratio of end diastolic interventricular septal thickness to end diastolic left ventricular posterior wall thickness, aortic root diameter, left atrial dimension, or frequency of aortic valve calcification or systolic anterior motion of the mitral valve with mitral-septal contact.

In the parasternal long axis view, D_1 was significantly longer (15 (5·0) *v* 10 (3·7) mm, $p < 0·001$, fig 4 left panel) and D_2 was shorter (11 (6·1) *v* 14 (3·9) mm, $p < 0·001$, fig 4 middle panel) in patients with aortic regurgitation than those without aortic regurgitation. The ratio of D_1 to D_2 was significantly greater in patients with aortic regurgitation than those without it (165 (72) *v* 74 (31)%, $p < 0·001$, fig 4 right panel). These data indicate that the basal septum protruded more into the left ventricular outflow tract, and the point of the septum that protruded most was closer to the aortic valve in patients with aortic regurgitation than in patients without it (fig 5).

REPRODUCIBILITY OF MEASUREMENTS OF D_1 AND D_2

Two independent observers repeated measurements of D_1 and D_2 to determine intraobserver and interobserver variability. Each observer measured D_1 and D_2 using an appropriate still frame without knowledge of his previous measurement or that of the other observer. Mean percentage intraobserver variability was 2% for D_1 and 3% for D_2. The correlation coefficient for D_1 was 0·98 and for D_2 it was 0·97. Interobserver variability (and correlation coefficients) for D_1 and D_2 were 4% (0·93) and 5% (0·88), respectively. Therefore, measurements of D_1 and D_2 can be performed with acceptable reproducibility.

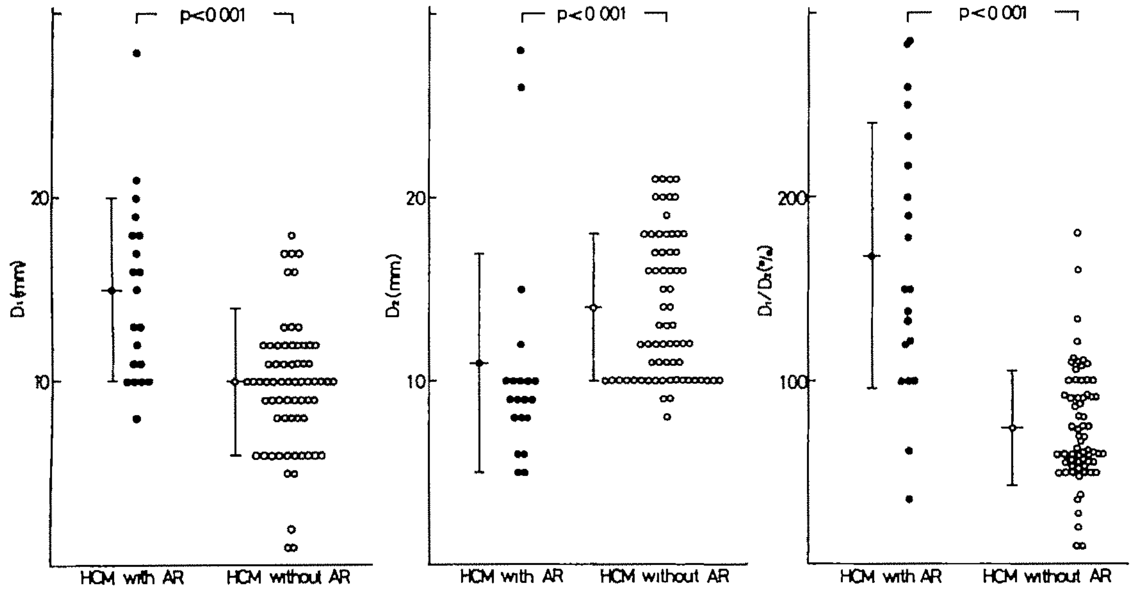

Fig 4 *D_1, D_2, and D_1/D_2 in patients with hypertrophic cardiomyopathy (HCM) who had aortic regurgitation (AR) and those who did not.*

Discussion

FREQUENCY AND SEVERITY OF AORTIC REGURGITATION IN HYPERTROPHIC CARDIOMYOPATHY

Teare and others have described diastolic murmurs in patients with hypertrophic cardiomyopathy.[8-10] Most of these reports, however, dealt with diastolic rumbles, presystolic murmurs, and third or fourth sounds. A high-pitched diastolic murmur caused by aortic regurgitation was rarely reported. Frank and Braunwald reported that seven of 126 patients with idiopathic hypertrophic cardiomyopathy had diastolic murmurs best heard at the apex in all.[11]

Barlow and Pocock described how aortic annular distortion caused by asymmetric myocardial hypertrophy led to aortic regurgitation in a few patients. The murmurs were soft and short and the regurgitation was slight.[12] However, the prevalence was not analysed statistically.

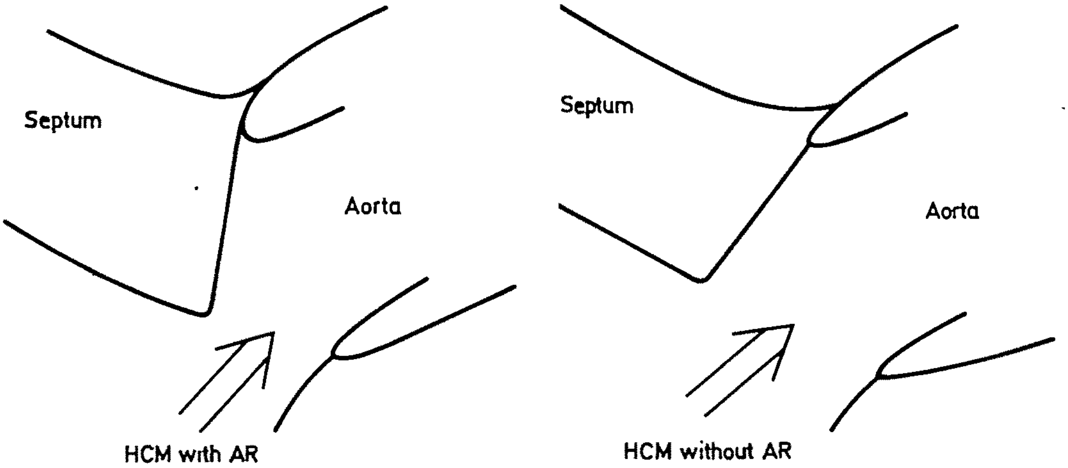

Fig 5 *Schematic model of the interventricular septum and aortic root based on the data of D_1 and D_2. The basal septum protruded more deeply into the left ventricular outflow tract and the point of the septum that protruded most deeply into the left ventricular outflow tract was closer to the aortic valve in patients with aortic regurgitation than in those without it. Arrows indicate the direction of ejection flow.*

In the present study, colour Doppler echocardiography showed that aortic regurgitation was not uncommon in patients with hypertrophic cardiomyopathy. Signals of aortic regurgitation were limited to the left ventricular outflow tract, suggesting that the degree of the regurgitation was mild. This is probably the reason why this association has rarely been detected by auscultation, phonocardiography, or conventional echocardiography. In 1987 Theard *et al* reported that conventional pulsed Doppler echocardiography detected mild aortic regurgitation in nearly a third of patients with hypertrophic cardiomyopathy.[5]

POSSIBLE CAUSE OF AORTIC REGURGITATION IN PATIENTS WITH HYPERTROPHIC CARDIOMYOPATHY

Barlow and Pocock suggested that morphological abnormality, that is, distortion of the aortic annulus caused by asymmetrical myocardial hypertrophy can result in aortic regurgitation.[12] The data on D_1 and D_2 and the ratio of D_1 and D_2 in the present study support this hypothesis, because the distortion of the aortic annulus is thought to be more pronounced in patients with aortic regurgitation than those without it.

The presence of systolic anterior motion of the mitral valve was not associated with aortic regurgitation in patients with hypertrophic cardiomyopathy. This is because the point of obstruction formed by the systolic anterior motion of the mitral valve is far from the aortic root and the impact of the jet stream to the aortic root may be weak. Yock *et al* recently reported that the high velocities of jets in the left ventricular outflow tract of patients with hypertrophic obstructive cardiomyopathy were generally not conducted to the aorta.[13]

There was no significant difference in ejection flow velocity immediately below the aortic valve measured by pulsed Doppler echocardiography between the patients with hypertrophic cardiomyopathy who had aortic regurgitation and those who did not. An eccentrically directed ejection flow caused by the interventricular septum that protruded deeply into the left ventricular outflow tract rather than flow velocity itself might be related to the cause of aortic regurgitation.

Although the exact cause of aortic regurgitation is uncertain, the morphological abnormality of the aortic root was related to the regurgitation.

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Cross sectional early mitral flow velocity profiles from colour Doppler

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SUMMARY Instantaneous cross sectional flow velocity profiles from early mitral flow in 10 healthy men were constructed by time interpolation of the velocity data from each point in sequentially delayed two dimensional digital Doppler ultrasound maps. This interpolation allows correction of the artificially produced skewness of velocities across the flow sector caused by the time taken to scan the flow sector for velocity recording of pulsatile blood flow. These results suggested that early mitral flow studied in an apical four chamber view is variably skewed both at the leaflet tips and at the annulus. The maximum flow velocity overestimated the cross sectional mean velocity at the same time by a factor of 1·2–2·2. Also the maximum time velocity integral overestimated the cross sectional mean time velocity integral to the same extent.

This cross sectional skew must be taken into account when calculation of blood flow is based on recordings with pulsed wave Doppler ultrasound from a single sample volume.

Pulsed wave Doppler has been used to record the flow patterns in non-stenotic mitral valves.[1-3] The method has an accurate time resolution, but the velocities are recorded from only a small area of the valve orifice. If the velocity varies across the orifice a recording from one sample volume may differ from the mean cross sectional velocity. Recently colour flow Doppler has been used to describe flow velocity patterns.[4-6] This method has accurate spatial resolution, but the poor time resolution might introduce errors in the measurement of pulsatile flow because of the sweep time across the flow sector, which is needed to update the colour flow maps.

To overcome the limited spatial information given by pulsed wave Doppler and the poor time resolution of colour flow Doppler a new method was developed. Digital Doppler ultrasound two dimensional flow maps, obtained with the ultrasound beam directed in parallel to the blood velocities, were used to construct instantaneous flow velocity profiles across the mitral orifice.

The technique was used to examine mitral flow in early diastole in healthy men. We examined these flow velocity profiles to estimate the error that may occur with pulsed wave Doppler when a limited sample volume is used to measure the mean velocity across the orifice.

Patients and methods

Ten healthy men, aged 12 to 42 years (mean 31 years), consented to the study. None had clinical, auscultatory, electrocardiographic, or echocardiographic evidence of heart disease.

The ultrasound measurements were made with a CFM 700 system (VingMed Sound). This is a combined cross sectional echocardiographic and two dimensional Doppler flow velocity system where the flow sector is constructed by colour coding the velocity information from 64 sample volumes along each of 64 sequentially transmitted ultrasound beams in each flow velocity map. The velocity in each sample volume is calculated by an autocorrelation function on the frequency and the intensity of the backscattered ultrasound signal.[7,8] We used a 3 MHz transducer with the high pass filter set at 21 cm/s, and by scrolling the baseline the upper velocity limit was 120 cm/s. The lateral resolution of the ultrasound beam, defined as a 50% decrease in

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backscattered signal from the centreline of the beam, was 2·1–2·5 mm at a depth of 8 cm from the transducer when the flow sector angle was set to 30°.

Each ultrasound beam is incrementally delayed relative to the preceding beam because of the time needed to send and receive several pulses before a new beam can be sent in the next direction. The sweep time of each flow map with a flow sector angle of 30° varies from 40 to 114 ms for different instrument set-ups and transducer. The actual sweep times are measured directly on the transducer controller inside the instrument. The flow sector can be moved by a track ball both laterally and radially in relation to the tissue sector. The width and the radial extension of the flow sector can also be adjusted while the 64 × 64 sampling volumes are maintained. The distances from the transducer to the areas of interest in the tissue and flow velocity maps are measured accurately by the analysis facilities of the instrument.

The men were examined in the left lateral recumbent position. The transducer was located at the apical window to give a four chamber view of the heart. Adjustment of the position and direction of the transducer and of the orientation of the flow sector reduced to a minimum the angle between the radial direction of the flow sector and the main direction of the mitral flow. The septal and lateral parts of the mitral annulus were visualised, and the sector plane was adjusted in the anterioposterior plane until optimal flow signals were obtained from the inflow channel. During data acquisition the patients were asked to stop breathing in passive end expiration with open airways.

Electrocardiographically triggered flow maps of the mitral area were made from sequential beats, and the start of the flow sweep relative to the R peak was increasingly delayed with increments of 20 ms from one beat to the next. The increases in sweep delay were adjusted manually. The first sweep was recorded before the start of passive atrioventricular flow and the last sweep after onset of flow caused by left atrial systole. The number of sweeps ranged from 13 to 19 (mean (SD) 16·1 (2·3)) in the ten men. The serial time gated recording of these flow sweeps obtained from each man was used for analysis of the flow patterns both at the mitral annulus and at the leaflet tips. None of the recording periods exceeded 25 seconds.

The ultrasound recordings were transferred to an external computer as raw Doppler data from the front end of the CFM 700 in real time or as digital velocity data from the replay memory of the instrument (fig 1). In addition, the recordings were stored on videotape.

In subjects 1 to 4, the raw colour Doppler data were transferred from the front end of the instrument via a custom made ultrasound data grabber and interface (PUDGI) to a Stride 460 computer (Stride Micro, Reno, NV). The raw two dimensional Doppler data were processed by a computer program that emulated the velocity estimation in the ultrasound instrument, and the velocity data were presented as a colour flow map displayed on a monitor or as velocity curves representing the velocities from each depth along an arc across the 64 beams. The velocity data were stored for further processing (fig 1).

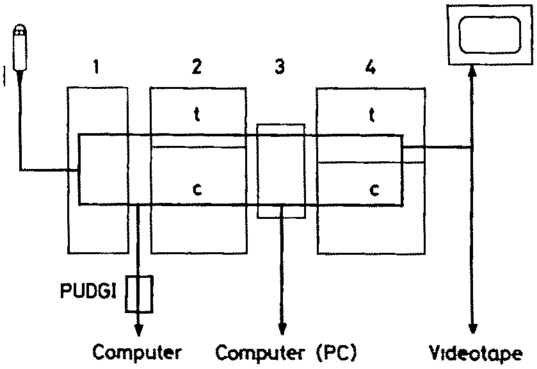

Fig 1 *Ultrasound system. Solid line represents the signal passage from the transducer (upper left) to the final presentation as cross sectional tissue and colour flow map on the monitor of the instrument (upper right). Four major levels of signal processing in the instrument are: (1) Instrument front end connected to the transducer. A custom made portable ultrasound data grabber and interface (PUDGI) capable of transferring the raw ultrasound data in real time to an external computer can be connected to the front end. The real time transfer of the ultrasound data enables post-processing of the raw digital Doppler flow data without its being influenced by the processing units of the instrument. (2) Data processing unit. The tissue data (t) and the Doppler colour flow data (c) are processed separately before the data are passed to the scan converter (4). (3) Digital replay memory with two megabyte storage capacity. The processed data on tissue and Doppler colour flow are passed to the replay memory of the instrument in parallel with the data transfer from the processing unit (2) to the scan converter (4). At this level the tissue and Doppler colour flow data are handled separately and the replay memory is continuously updated as new data are passed through the system, with a simultaneous erasing of the oldest data in the memory. In freeze mode of the instrument the content of the digital replay memory can be replayed from the monitor for measurements and tape recording. These data can also be transferred to an external computer for the analysis performed in this article. (4) Tissue and colour flow images are mixed in the scan converter for combined presentation on the monitor. The Doppler colour flow sector is overlayed on the tissue sector from the same transducer sweep cycle.*

The recordings from subjects 5–10 were transferred from the replay memory of the ultrasound instrument to an external computer (IBM PC compatible). At this level of data processing the Doppler data are available as digital velocity information from each of the 64 times 64 points of the flow sector from each recorded map. The selected number of consecutively recorded maps from each patient could be transferred by custom software in the ultrasound instrument. The velocities along an arc of the 64 beams at defined depths from the recordings could also be transferred from these files to a standard data file for further processing.

These standard data files, containing information on the instrument set-up as well as the digital Doppler data, were loaded into a commercial spreadsheet program (Microsoft Excel, Microsoft Corporation) where the calculations needed to correct for the sweep time and generate undistorted velocity profiles were made.

In some of the recorded maps, velocity data from some points along the arc of the ultrasound beams were missing. These "holes" were regarded as artefacts introduced by the instrument. The missing values were corrected in the spreadsheet program by comparing the velocity data close to the "hole" and replacing the missing values with the average of the two neighbouring values from the same sweep before the time interpolation procedure.

Both transfer procedures give rapid collection of high quality flow velocity data unaffected by errors introduced by the display system, video recorder, or re-digitisation of a colour coded display.

Any of the 64 arcs across the flow sector can be used to generate velocity profiles. The depth from the transducer to the displayed cardiac structures of the tissue sector can be measured from the actual recording by the replay memory of the instrument.

Since the mitral flow is pulsatile, the sweep time from one side of the flow sector to the other distorts the velocity profiles constructed from arcs of sample volumes across the flow sector. To compensate for this distortion, data obtained from sequentially delayed flow sweeps were interpolated. Each sweep of the ultrasound beam was triggered by the R wave of the electrocardiogram. Consecutive sweeps were delayed by 20 ms in relation to the previous one (fig 2 b and c). We excluded recordings where the RR intervals of the various heart cycles deviated more than 20 ms from the median.

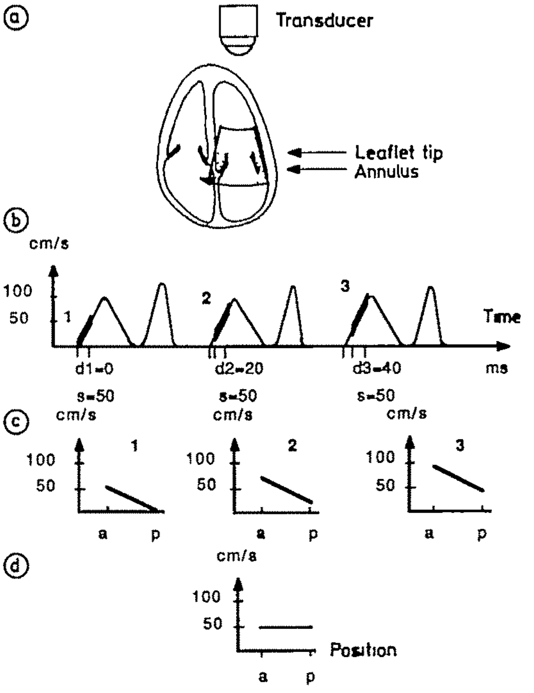

Fig 2 *(a) Schematic drawing of the heart in apical four chamber view. The mitral flow velocity distribution in this example is assumed to be flat. The ultrasound Doppler two dimensional sector is 30°; the two dimensional Doppler ultrasound sweep direction is from right to left, sweep time = 50 ms. Horizontal arrows indicate the depths of cross sectional flow profiles in this study. (b) Pulsed wave Doppler recording of the pulsatile flow in the mitral orifice at both levels with overlayed velocity changes during a recording period (s) of 50 ms, and where the recording period is sequentially delayed (d) by 20 ms relative to the flow start from one flow period to the other; dl = 0 ms, d2 = 20 ms, and d3 = 40 ms. (c) Velocity traces across the width of the mitral orifice in panel (a) as obtained when recorded with the ultrasound Doppler two dimensional system. Velocities are given along the y axis and the position in the mitral orifice along the x axis (a = anterior leaflet, p = posterior leaflet). Numbers 1 to 3 represent sequentially delayed two dimensional sweeps of the flow pulses 1 to 3 in (b). The duration of each sweep is 50 ms. Note the artificial skewing caused by the lag in data collection. (d) Instantaneous flow velocity distribution across the width of the orifice in panel (a). Velocities are given along the y axis, and position in the mitral orifice along the x axis (a = anterior leaflet, p = posterior leaflet). This flow profile is calculated by linear time interpolation of the velocity traces 1 to 3 in panel (c), at 50 ms from start of flow.*

Thus the position and velocity information from each point along the selected arcs relative to the R wave of the electrocardiogram were known for each flow sweep, and linear interpolation between the velocities from each of the sequentially delayed recordings was done. The interpolation varied across the arc to adjust for the sweep time and resulted in an estimate of the cross sectional flow profile at a single point in time (fig 2d). Since the time lag of the updating of the colour flow map is compensated for by the calculation procedure, we called this calculated cross sectional flow velocity distribution *the* *instantaneous flow velocity profile.* An instantaneous flow velocity profile could be calculated for any time in the flow cycle and at any depth of the two dimensional Doppler flow velocity sector and the results displayed as a three dimensional plot for each depth (fig 3). We calculated the instantaneous flow velocity at the leaflet tips and at the mitral annulus in all 10 men, and measured the actual depths at the time of maximum separation of the mitral leaflets in early diastole.

STATISTICAL ANALYSIS

Results are given as ranges and sample means (SD).

Results

The results were plotted as velocity profiles versus time to give a three dimensional presentation of the data. The profiles were to some extent skewed in all subjects, both at the annulus and at the tip of the mitral valve leaflets. The plots in fig 3 show different orientations of the skew in two patients. In patient 2 the skew is toward the posterior leaflet, while in patient 7 the skew is toward the anterior leaflet. At the level of the annulus the highest velocities were recorded anteriorly in both men.

The maximal instantaneous velocity versus the simultaneous cross sectional mean velocity gives an indication of the degree of skewness at the time of peak flow. The difference between maximum velocity and cross sectional mean velocity at the leaflet tips varied from 14 cm/s in subject 2 up to 41 cm/s in subject 6 (table). The mean differences for all subjects were 24·4 cm/s and 23·1 cm/s at the level of the leaflet tips and at the annulus respectively. Figure 4 shows the relative locations of the maximum velocity within the valve orifice and the maximum velocity as a proportion of the cross sectional mean velocity at the same time for each man at the levels of the leaflet tips and the annulus.

The time velocity integral is the integral of velocity over time for a specific point in the arc. This is the value used to estimate volume flow when recording with pulsed wave Doppler from a single sample

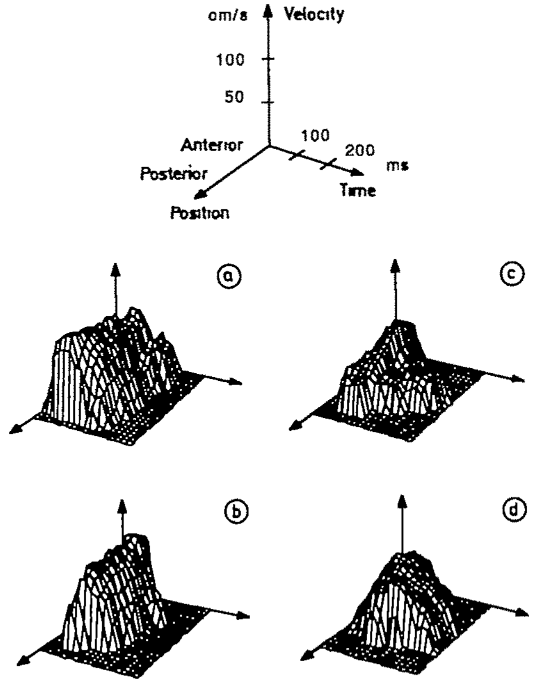

Fig 3 *Plots of instantaneous early mitral flow velocity profiles against time. Axis scaling and orientation are shown at the top of the figure. Plots a and b are from subject number 2, recorded from the level of the leaflet tips, (a) and at the level of the mitral annulus (b). Plots (c) and (d) are from subject number 7 at the level of the leaflet tips and annulus respectively. In these two healthy men the instantaneous flow profiles at the leaflet tips are skewed, but the maximum velocities are at different positions in the valve orifice—in subject 2 at the posterior leaflet and in subject 7 at the anterior leaflet. The velocity profiles were skewed at the level of the mitral annulus in both men, but the highest velocities were recorded at the anterior leaflet.*

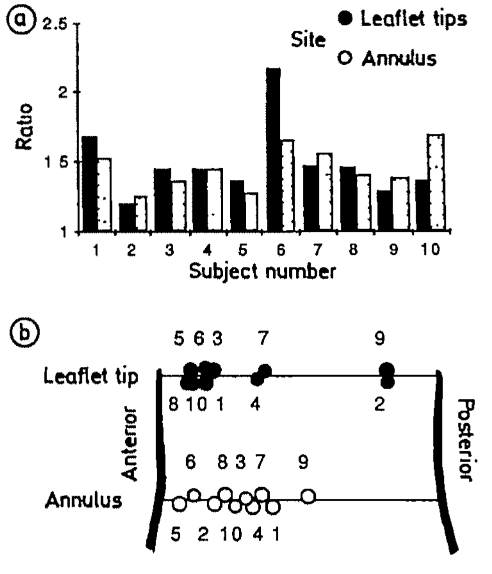

Fig 4 *(a) Ratio of the maximum velocity to the mean cross sectional velocity at the time of maximum flow velocity of early mitral flow, at the leaflet tips (solid bars) and at the annulus (patterned bars). (b) Site of the maximum velocity within the mitral orifice is shown for each subject at the level of the tips (solid dots) and the annulus (open circles). Leaflet margins are indicated as solid vertical lines.*

Table *Maximum flow velocity and time-velocity integral of early mitral inflow compared with the simultaneous mean velocity and mean time-velocity integral across the mitral orifice at the level of the leaflet tips and the annulus*

			Velocity (V) (cm/s)				*Time-velocity integral (I) (cm)*			
			Tip		*Annulus*		*Tip*		*Annulus*	
No	*Age (yr)*	*HR (beats/min)*	*Max V*	*Mean V*	*Max V*	*Mean V*	*Max I*	*Mean I*	*Max I*	*Mean I*
1	38	55	59	36	80	57	6·2	3·7	7·5	4·9
2	42	41	79	65	82	65	12·0	10·0	11·0	8·7
3	32	76	70	33	57	34	6·8	4·7	5·6	4·1
4	28	67	50	32	55	26	8·1	5·6	6·8	4·7
5	42	60	80	57	67	51	10·3	7·6	7·7	6·0
6	33	68	75	34	66	39	11·3	5·2	10·0	6·0
7	28	56	55	37	58	37	6·8	4·6	7·5	4·8
8	34	59	73	54	77	52	10·1	6·9	7·2	5·1
9	25	58	80	60	82	66	11·1	8·6	8·9	6·4
10	12	74	77	46	74	40	8·7	6·4	8·3	4·9
Mean	31	61	69·8	45·4	69·8	46·7	9·1	6·3	8·1	5·6
SD	9	10	11·1	12·6	10·6	13·5	2·1	2·0	1·6	1·3

Tip, measurements at the level of mitral leaflet tips; annulus, measurements at the level of the mitral annulus; HR, heart rate; Max V, maximum velocity of the early mitral flow, Mean V, cross sectional mean velocity at the time of maximum velocity at the defined level, Max I, time velocity integral from the point in the flow sector at the defined level giving maximum value of early mitral flow; Mean I, mean cross sectional time velocity integral of early mitral flow at defined depth in the flow sector.

volume. The maximum time velocity integral is the maximum found for a given arc. The mean time velocity integral is the arithmetic mean of the integral values across this arc.

The difference between the maximum and the simultaneous cross sectional mean time velocity integral varied from 1·5 cm at the annulus in subject 3 up to 6·1 cm at the leaflet tips in subject 6 (table). The mean differences for all subjects were 2·8 cm at the leaflet tips and 2·5 cm at the annulus. Figure 5 shows the ratio of the maximum integral to the mean time velocity integral, and the relative location of the maximum integral within the orifice for each man at the levels of the leaflet tips and the annulus.

Heart rate ranged from 41 to 76 (men 61 (10)) beats per minute (table). All men were in sinus rhythm.

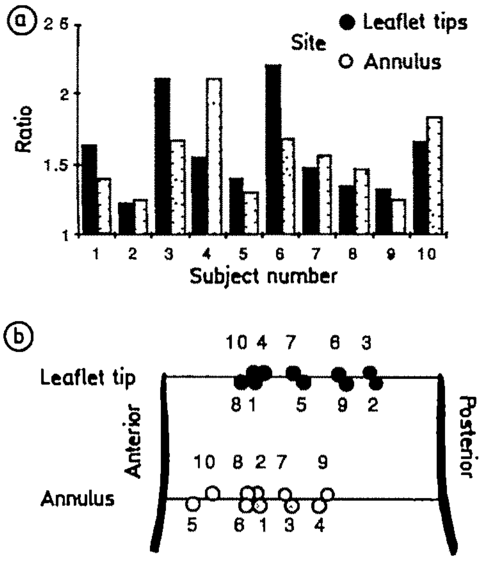

Fig 5 *(a) Ratio of maximum time-velocity integral to the mean cross sectional time-velocity integral of early mitral flow at the leaflet tips (solid bars) and at the annulus (patterned bars). (b) Site of the maximum time-velocity integral within the mitral orifice is shown for each subject at the level of the tips (solid dots) and the annulus (open circles). Leaflet margins are indicated as solid vertical lines.*

Discussion

The results indicated that the velocity profiles, both at the tips of the mitral valve leaflets and at the annulus, are skewed to a variable degree during the early phase of the mitral flow. At the time of peak flow, the highest velocities were 1·2 to 2·2 (tip of the leaflets) and 1·2 to 2·1 (annulus) times higher than the cross sectional mean velocity. Similar results were found when the highest time-velocity integral was compared with the mean time-velocity integral across the orifice, indicating that the profiles were skewed to some extent throughout the early phase of the mitral flow. There were no clear differences in the degree of skewness at the tip of the leaflets and at the annulus. The average overestimation of the mean velocity integral that would occur if the maximal integral had been used was 49% at the tip of the leaflets and 46% at the annulus. The standard deviation, however, was larger at the tip of the leaflets (27% *v* 15%).

The orientation of the skew within the valve apparatus varied between individuals and in some men between the annulus and the leaflet tips (fig 4); it also varied with time (fig 3). This observation suggests that the recording of maximum flow velocity with pulsed wave Doppler ultrasound should not be guided by the location in the valve orifice at a defined depth, but by the observed maximum velocities only.

In one of the men (number 1, table) we found a higher maximum flow velocity at the mitral annulus than at the leaflet tips. This is in contrast with what is usually found with pulsed Doppler in patients and might possibly be explained by the suboptimal orientation of the plane of the sweep sector because both cross sectional profiles were obtained from the same sweeps. The small difference in maximum velocities between the annulus and the leaflet tips in four of the other men may similarly have been caused by a suboptimal anterioposterior orientation of the plane of the flow sector, but might also be explained by small differences in orifice size at the two locations.

Few attempts have been made to measure the velocity profiles of mitral flow because its location within the heart makes it difficult to measure. Invasive procedures may interfere with valvar or ventricular function and this may affect the mitral flow pattern.

We are aware of only one previous published study on the velocity profiles of mitral flow.[9] Taylor and Whamond used a Pitot needle to study flow through the mitral orifice in dogs. They reported fairly flat profiles of early mitral flow both at the annulus and at the tip of the valve leaflets. Taylor's results and our own may differ because we studied different species and used different techniques.

Previous estimates of volume flow based on measurements of flow velocity and flow area at the level of the mitral valve assumed a flat velocity profile.[10 11] Our results suggest that values based on the maximum time velocity integral tend to overestimate the mean integral. The inconsistency of the results of different studies may partly be explained by our findings of a non-flat velocity profile and partly by inaccuracies in measurements of the effective flow area.[12-15]

APPLICATIONS

Colour flow Doppler provides a new way of evaluating velocity profiles within the heart because the velocity information from sample volumes located along an arc at a certain depth can be analysed. The advantage of this method is that the ultrasound beam can be oriented almost in parallel with the flow velocity. The resulting cross sectional velocity profiles will thus contain more accurate velocity information. However, the main problem is that these velocity profiles will be skewed when recordings are made of accelerating flow because of the time taken to scan the flow sector.

There are several reports on flow topography based on Doppler two dimensional flow recordings.[4-6] One of them was an in vivo study in which the time lag of the colour Doppler technique may have introduced errors because of the changes in flow velocity during each flow scan.[5] So far the timing of the colour flow sweep in relation to the events during the cardiac cycle has been discussed only in relation to regurgitation jets.[16 17]

The present method avoids the distortion of the velocity profile caused by the time lag, making it possible to obtain accurate velocity profiles at different sites within the heart. This has important implications for volume flow calculations, especially in regurgitation and with shunts.

OTHER METHODS

Multigated Doppler ultrasound has been used by some.[18 19] But with this method the flow velocity has to be recorded nearly perpendicularly to the direction of the ultrasound beam to read the flow velocity profile across the width of a flow channel. This is a disadvantage because errors in the velocity estimate increase as a function of the cosine of the angle between the blood flow and the ultrasound beam.

Magnetic resonance techniques for velocity mapping have been used on the ascending and descending aorta in healthy individuals,[20 21] but so far flow velocity profiles across the mitral orifice have not been reported.

In experimental settings different methods have been used, including the Pitot principle[9] and hot film anemometry,[22 23] but the invasiveness of these methods limits their use in patients. Pulsed wave Doppler ultrasound, with the ultrasound beam directed in parallel with the blood flow direction, has been used to measure flow in the ascending aorta during operation.[24]

LIMITATIONS OF THE METHOD

The main limitation of the method used in the present study was that the profiles were evaluated in only one plane and from only one sequence of time gated recordings in each man. This may explain why the highest velocities were recorded at the annulus in some men. At the tip of the leaflets the highest velocities may have been outside the plane of the colour flow sector. This limitation can be overcome by stepwise rotation of the transducer to construct a series of profile maps. With current instruments and software such a procedure would be too time consuming.

Because the streamlines of the mitral flow probably ran in parallel, at least during part of diastole, and the ultrasound beams making up the Doppler colour sector did not, the angle of incidence between the flow and measurement direction varies from one side of the flow area to the other. To minimise the error on profile calculations we attempted to align the centreline of the Doppler sector with the centreline of the flow. A sector angle of 30° was sufficient to cover the mitral flow in the region of interest, limiting the maximum angle of incidence to about 15%. Accordingly, an error on velocity estimates should be less than 6%. When the velocity pattern is more complicated (that is the streamlines are not parallel) or when the vector of the velocities is out of the plane of the flow velocity sector the error may be larger.

The velocity estimates at each point in the two dimensional flow map are based on calculations of the Doppler shift of the received signal from each point in the sector. In conventional Doppler recordings, fast Fourier transformation is used to give a spectrum display as well as maximum and mean estimates. Because the two dimensional flow technique has a much faster rate of data acquisition than conventional Doppler, more efficient processing of the data is required. The algorithm used by the instrument is based on calculation of the centre frequency (that is the mean frequency of the Doppler spectrum from each point in the flow sector) and intensity of the received signal based on an autocorrelation technique. If flow is not disturbed this method gives accurate velocity estimates.[7, 8]

The lateral resolution of the system caused two neighbouring points in the three dimensional plots to overlap at a position where the power of the backscattered signals was reduced to 60% of the maximum power centrally in each beam (fig 3). The influence of points that were further apart was not significant. Hence the resolution of the three dimensional plots was regarded as appropriate.

The high pass filter of the instrument used was set at 21 cm/s, which means that velocities below this limit were not recorded. The upper velocity range is limited by the Nyquist frequency.[25] However, by moving the baseline this limit can be increased up to two times the Nyquist velocity minus the high pass filter velocity limit. We used a 3 MHz transducer with an upper velocity limit of 120 cm/s.

The two different routines for transferring the digital ultrasound data from flow sweeps introduced no differences in the calculation of flow velocities because both methods used the same algorithm to calculate velocity. Also we calculated the instantaneous flow velocity profiles in the same way in all the men—by linear time interpolation between the acquired data from the sequentially delayed flow maps.

SOURCES OF ERRORS

Because the recording technique samples data from several heart beats it requires exact aiming, without transducer movement during the recording period. Thoracic movement and changes in mitral flow volume caused by respiration were likely to introduce errors. So the men were asked to stop respiration in passive end expiration with open airways during data acquisition.

Changes in the selected depth of sampling caused by volume filling of the left ventricle during the recording period were not corrected because the change in location of the mitral annulus within the two dimensional flow sector was considered to be small during early diastole.

Irregularities in heart rate and rhythm, as well as the increment in the sequentially delayed two dimensional flow maps relative to the trigger marker (the R wave of the electrocardiogram signal), could also introduce errors in calculations of the instantaneous flow velocity profile.

To reduce these sources of error we checked all recordings for inaccuracies by replaying video recordings. Because the two dimensional tissue sector is updated immediately before the two dimensional flow map, changes in tissue and flow sectors relative to the heart from one heart beat to the other could be monitored.

CONCLUSIONS

The use of digital flow velocity information from two dimensional Doppler flow maps of the early mitral flow, using time interpolation of the acquired data from sequentially delayed flow maps, provides a new method for calculation of instantaneous flow velocity profiles.

The results from our study give new information on the distribution of mitral flow velocity across the width of the mitral valve at the levels of the leaflet tips and at the annulus in the human heart. This shows that the instantaneous flow velocity profiles are variably skewed at both sample depths in an apical four chamber view. A skewed profile of early mitral flow velocity should be borne in mind when recordings from a small area in the valve orifice are used for volume flow calculations; this skewness may result in significant errors.

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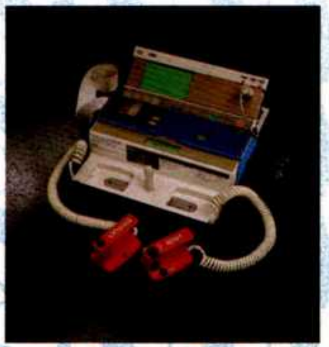

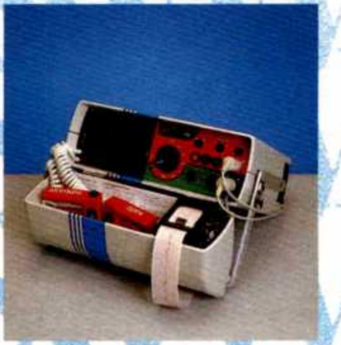

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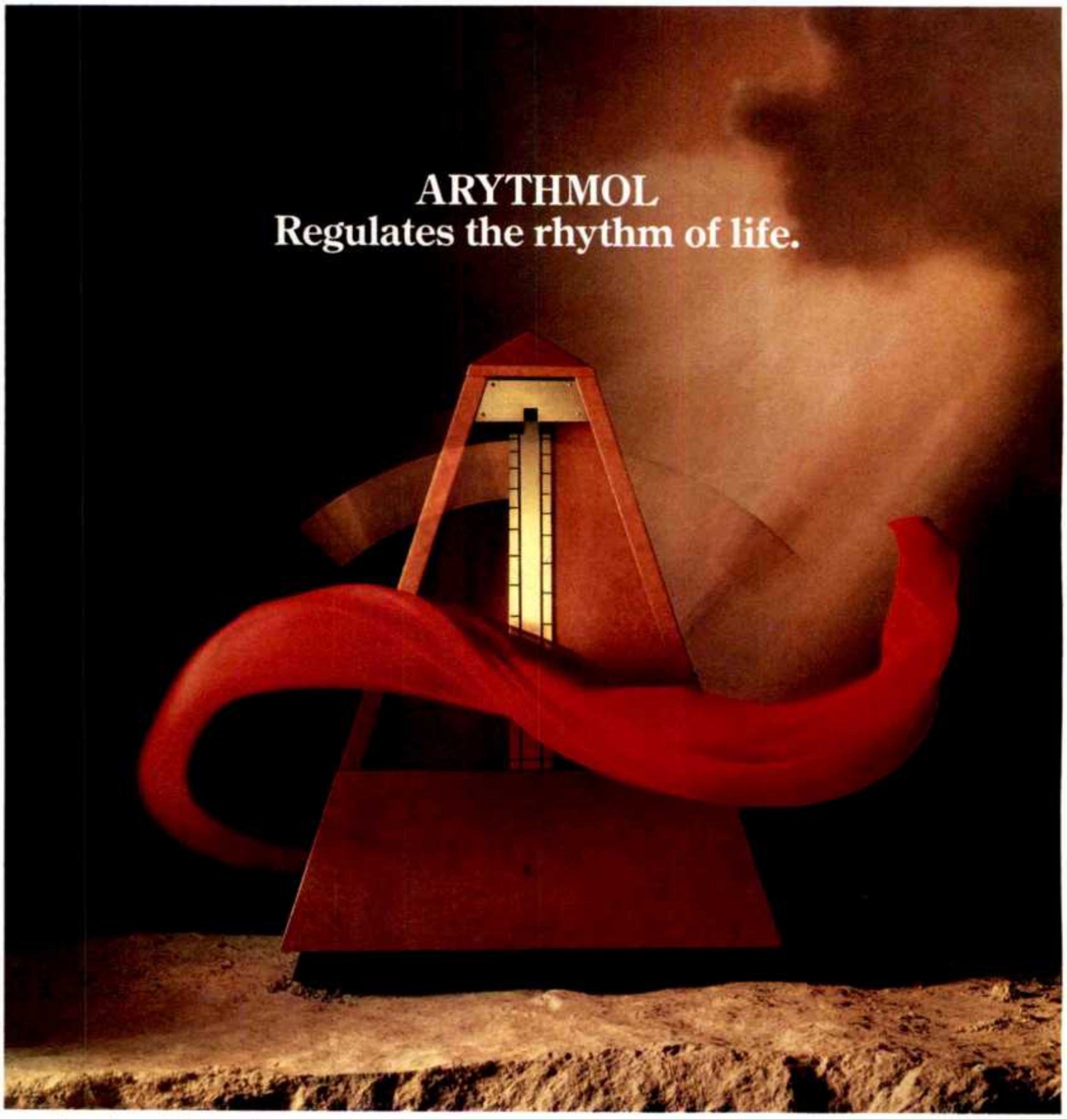
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Subclinical cardiac dysfunction in acromegaly: evidence for a specific disease of heart muscle

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SUMMARY Acromegaly is associated with an increased cardiac morbidity and mortality, but it is not clear whether this is the result of increased incidence of hypertension and coronary heart disease or of a specific disease of heart muscle. Thirty four acromegalic patients were studied by non-invasive techniques. Seven of these patients had raised plasma concentrations of growth hormone at the time of study; three were newly diagnosed and had not received any treatment. Hypertension was present in nine (26%) but only three (9%) had electrocardiographic left ventricular hypertrophy. Echocardiography showed ventricular hypertrophy in 12 (48%) and increased left ventricular mass in 17 (68%) patients. Holter monitoring detected important ventricular arrhythmias in 14 patients. Thallium-201 scanning showed evidence for coronary heart disease in eight patients. Systolic time intervals were normal except when there was coexistent ischaemic heart disease. A comparison between 19 acromegalic patients with no other detectable cause of heart disease and 22 age matched controls showed appreciably abnormal left ventricular diastolic function in the group with acromegaly. The abnormalities shown did not correlate with left ventricular mass or wall thickness. There was no difference in diastolic function between patients with active acromegaly and those with treated acromegaly. Hypertensive acromegalic patients had worse diastolic function than hypertensive controls, suggesting that hypertension may further impair the left ventricular diastolic abnormality in acromegaly.

This is the first study to find evidence of subclinical cardiac diastolic dysfunction in acromegaly and it supports the suggestion that there is a specific disease of heart muscle in acromegaly.

While systemic hypertension, atherosclerosis, and diabetes mellitus may contribute to cardiovascular complications in acromegaly, cardiac failure has occurred in patients with acromegaly in the absence of these and other established causes of heart muscle disease.[1-5] Such cases suggest the existence of a specific disease of heart muscle in acromegaly. Postmortem studies showed an "abnormal myocardium" in 59% of cases of acromegaly and "definite myocarditis" in 26%,[6] suggesting that cardiac dysfunction may be more common than clinical examination alone suggests. Although Jonas *et al* found abnormal systolic time intervals in six of 10 patients with acromegaly,[7] more recent studies with radionuclide angiography showed no abnormality of left ventricular systolic function unless other cardiac disease was present.[8 9]

There is mounting evidence that radionuclide measurements of diastolic function are more sensitive than measurements of ejection fraction, not only in the detection and therapeutic assessment of coronary heart disease[10-12] but also in patients with left ventricular hypertrophy, which produces abnormal relaxation of the ventricle.[13-15] These non-invasive measurements of diastolic function correlate well with measurements obtained invasively at cardiac catheterisation.[16]

We used non-invasive methods to look for evidence of a specific disease of cardiac muscle in patients with acromegaly in whom other recognised causes had been excluded.

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Patients and methods

PATIENTS

We studied 34 consecutive patients with a firm diagnosis of acromegaly. The diagnosis was based on clinical features and a resting, fasting serum concentration of growth hormone of > 10 mU/l which was not suppressed by a 50 g oral glucose load. Table 1 summarises the clinical characteristics of the patients. None of the patients had symptomatic ischaemic heart disease or evidence of heart failure at the time of study.

CONTROLS

Control data were obtained from 22 healthy volunteers with no history of cardiorespiratory disease. They were normotensive and had a normal physical examination, a normal resting electrocardiogram, and a negative maximal graded treadmill exercise test. We compared radionuclide angiographic data from the age matched controls at rest and during exercise with the data from the patients with acromegaly.

ESSENTIAL HYPERTENSION

We compared 14 age matched patients with essential hypertension with the hypertensive acromegalic patients. These 14 patients were symptom free, had normal electrocardiograms at rest and on exercise, normal wall motion on radionuclide angiography, and were on no medication at the time of the study.

CLINICAL ASSESSMENT

We took a detailed history from each patient before physical examination for clinical evidence of ischaemic heart disease, thyroid disease, excess alcohol consumption, and concomitant illness. Drug medication and the duration of acromegaly were recorded. Blood pressure was measured twice with the patients lying and standing and after five minutes of supine rest. Patients whose blood pressure was > 160/95 mm Hg when they were lying down were considered to have hypertension. Patients with a history of hypertension who were on antihypertensive treatment were regarded as having hypertension, even if blood pressure readings at the time of the clinical assessment were < 160/95 mm Hg.

Table 1 *Clinical details of patients with acromegaly*

Patient No	*Age/sex*	*Hypertension*	*ECG*	*Time since treatment (yr)*	*Type of treatment*	*Growth hormone concentration (mU/l)*
1	56 F	−	N	6	HYP	1 7
2	48 M	+	N	4	HYP, DXT	10·6
3	51 M	−	N	9	HYP	1·9
4	62 M	−	N	12	HYP	<1 9
5	63 F	+	N	4	B	6·4
6	59 M	−	RBBB	8	HYP, B	<1·0
7	52 M	−	N	5	HYP	1·1
8	61 M	−	LBBB	6	B	2·7
9	37 M	−	N	9	HYP	2·3
10	53 M	+	LVH	8	HYP	<1 0
11	64 F	−	N	5	HYP	8·3
12	65 F	−	N	8	HYP	5·9
13	49 M	−	N	8	HYP	<1·0
14	35 F	−	N	7	HYP, B	3 2
15	54 M	−	N	11	HYP	1·6
16	66 F	−	N	12	B	8·6
17	62 M	−	N	9	HYP	<1·0
18	58 M	−	N	10	HYP	1·7
19	41 F	−	N	12	HYP, DXT	4·3
20	60 F	+	N	5	HYP	<1·0
21	56 M	−	N	4	HYP	4·6
22	65 M	+	RBBB	6	B	4·0
23	64 F	−	N	10	HYP	4 7
24	42 M	−	N	5	HYP	<1 0
25	68 M	+	LBBB	10	DXT	12·1
26	58 F	−	N	5	HYP	14 0
27	28 M	+	LVH	5	HYP	37·0
28	50 F	−	N	Pre-op	B	39·0
29	65 M	−	N	6	DXT, HYP	18·7
30	70 F	+	LVH	Pre-op	—	40·2
31	46 M	−	N	Pre-op	—	41·1
32	72 M	−	N	7	Nil	70 5
33	53 M	−	N	14	HYP	22·4
34	64 F	+	N	12	HYP, B	15 8

B, bromocriptine; DXT, radiotherapy; HYP, hypophysectomy; N, normal; LBBB, left bundle branch block; RBBB, right bundle branch block; LVH, left ventricular hypertrophy.

Blood was withdrawn for the measurement of serum concentration of growth hormone, thyroid function tests, serum creatine kinase concentration, random blood glucose, and for liver function tests, including γ-glutamyl transpeptidase.

ELECTROCARDIOGRAPHY

A standard 12 lead electrocardiogram was performed on each patient and evidence of old myocardial infarction, left ventricular hypertrophy, or conduction abnormalities was sought. Patients then underwent a maximal, symptom limited, graded treadmill exercise test with a modified Chung protocol; the bipolar electrocardiographic leads CM5 and CC5 were monitored during the test.[17] Horizontal or downsloping ST segment depression of >1 mm at 80 ms from the J point was regarded as evidence of ischaemia.

AMBULATORY ELECTROCARDIOGRAPHIC MONITORING

Twenty four hour electrocardiographic monitoring (Oxford Medilog) was performed to detect rhythm disturbances and the tapes were analysed with a Reynolds Medical Pathfinder and visual supervision.

SYSTOLIC TIME INTERVALS

We measured systolic time intervals on a multichannel Cambridge recorder at a paper speed of 100 mm/s from simultaneous recordings of the electrocardiogram, carotid pulse tracing, and phonocardiogram. We recorded high frequency phonocardiograms with a piezoelectric microphone positioned on the precordium to display optimally the aortic component of the second heart sound. Carotid pulse tracings were obtained with a hand held funnel pick up that was air coupled to a crystal transducer. The electrocardiographic lead showing the earliest onset of the QRS complex was used for measurements. A mean of three values for pre-ejection period, left ventricular ejection time, and hence the ratio were derived according to the method described by Weissler and Garrand.[18]

THALLIUM-201 SCINTIGRAPHY

At symptom limited peak exercise a bolus of 74 MBq thallium-201 was injected through an indwelling forearm venous cannula and exercise was continued for a further minute. Scintigrams were obtained in the anterior, left anterior oblique, and lateral views and scanning was repeated 4–6 hours later with a cardiac gamma camera (Elscint 215M) equipped with a low energy, all-purpose collimator with an energy window of 20% around the 80 keV photopeak of thallium-201. The scintigrams were reported "blind" by two trained observers without knowledge of the patient's clinical or laboratory findings. After subtraction for background a region of interest was placed around the left ventricle and a semiquantitative program was used to obtain counts from five different segments of the left ventricle. Segmental perfusion abnormalities were classified as fixed or reversible according to previously established criteria.[19–21]

Ischaemic heart disease was considered to be present if any of the following was present: (*a*) documented myocardial infarction; (*b*) angina pectoris with ST/T wave abnormalities on a resting 12 lead electrocardiogram; (*c*) presence of >1 mm horizontal or downsloping ST segment depression 80 ms after the J point on exercise testing associated with the demonstration of a fixed or reversible perfusion defect on thallium-201 scintigraphy; (*d*) reversible perfusion defect on thallium scintigraphy even in the absence of significant ST segment depression on exercise testing.

ECHOCARDIOGRAPHY

We attempted to get a cross sectional echocardiogram in all patients with a Diasonics V-3400R real time, phased array imaging system coupled to a 2·5 MHz transducer. Scans were obtained in the standard views in order to examine the aortic and mitral valves. We then obtained a derived M mode recording of the left ventricle at a paper speed of 25 mm/s, having adjusted the transducer to obtain optimal recordings of both the interventricular septum and left ventricular posterior wall. The M mode scan at the level of the chordae tendineae was used to measure left ventricular end diastolic and end systolic dimensions, and the thickness of the interventricular septal wall and left ventricular posterior wall. Mean values from three cardiac cycles were used for calculation. From these values we calculated left ventricular mass using the formula of Devereux and Reichek.[22]

Analysis of the echocardiograms was carried out without knowledge of the clinical or laboratory findings.

RADIONUCLIDE VENTRICULOGRAPHY

Equilibrium radionuclide ventriculography was performed at rest with individuals in the supine position, after in vivo labelling of red blood cells with stannous pyrophosphate (Pyrolite) and 740 MBq of technetium-99m. Imaging was performed with a mobile gamma camera (Elscint Model 215M) in the left anterior oblique (best septal) projection. Electrocardiographic gating was used to collect and organise the data into a series of 32 frames for each cardiac cycle in order to obtain a high resolution left ventricular time-activity curve.

Cardiac cycles falling outside a pre-selected range of acceptable cycle lengths were automatically excluded from analysis by setting an RR triggering tolerance of 5%; this prevented distortion of the time-activity curve by variation in cycle length. By excluding long or short cycles, the portion of the time-activity curve describing diastolic events was accurately preserved. Five million counts were collected and the data were stored in a 64 × 64 matrix on a dedicated computer. After nine point smoothing and time correction, left ventricular regions of interest were drawn by a computer derived counts based method. A second derivative edge defining algorithm based on a Fourier and amplitude model was used to identify the left ventricular contour in each of the 32 frames.[23] After background subtraction a high resolution time-activity curve was differentiated and from the curve the point of peak filling rate was identified. Exercise radionuclide studies were performed in supine patients and volunteers using methods described in detail elsewhere.[24-26]

Global left ventricular systolic function was assessed by the ejection fraction, ejection rate, and ejection time. Peak filling rate, time to peak filling rate, early filling rate, and first one third filling fraction were used to describe left ventricular diastolic function.[11 12 14 24-26]

Each investigation was reported blindly by trained observers without knowledge of the patient's clinical or laboratory findings or the results of the other tests.

The study was approved by the hospital ethics committee and patients and volunteers gave written informed consent before participating. We used two tailed unpaired Student's *t* tests and linear regression analysis for statistical analysis.

Results

We studied 34 patients (21 men and 13 women, mean age 56 years (range 28–72)) with past or present acromegaly. In seven plasma concentrations of growth hormone were raised at the time of study. Other pituitary function was normal at the time of study; however, seven were receiving steroid replacement and three thyroxine replacement therapy. Liver function tests were normal in all patients. None had evidence of diabetes mellitus. Table 1 summarises the cardiovascular state of the patients. Hypertension was present in nine (26%), none had electrocardiographic evidence of old myocardial infarction, and in only three (9%) were Romhilt and Estes's electrocardiographic criteria[27] for left ventricular hypertrophy fulfilled. All patients were in sinus rhythm at the time of study. There were conduction abnormalities on the resting electrocardiogram in four (12%). A total of 14 had evidence of hypertension or ischaemic heart disease or both. One patient (case 23) who had an inconclusive exercise test and who did not undergo thallium scintigraphy or a wall motion study was excluded from analysis.

EXERCISE TESTING

Only one patient stopped exercising because of anginal pain. Fatigue was the end point in 17 and breathlessness in 15. Five achieved the target heart rate and stopped because of fatigue. Five had positive ST segment criteria for ischaemia but all of these had normal exercise and redistribution thallium-201 scans and normal wall motion on radionuclide ventriculography.

AMBULATORY ELECTROCARDIOGRAPHIC MONITORING

Arrhythmias were detected in 14 patients. The most common finding was asymptomatic isolated ventricular extrasystoles. One of these patients (case 27) had prolonged asymptomatic episodes of ventricular bigeminy. In another patient runs of ventricular tachycardia were recorded, which were producing symptoms of palpitation and dizziness (case 8). This patient had left bundle branch block on the resting electrocardiogram, abnormal wall motion on radionuclide ventriculography, and a reversible perfusion defect on thallium scintigraphy; it was therefore deduced that he had ischaemic heart disease. Two patients (cases 13 and 25) had sinus pauses and in one of these (case 13) asymptomatic pauses of up to 4·4 seconds were recorded at night.

SYSTOLIC TIME INTERVALS

According to the normal range (0·25–0·41) defined by Martins *et al*[8] systolic time intervals were abnormal at rest in only three (9%); all had other evidence of ischaemic heart disease with dilated left ventricles. Systolic time intervals were only abnormal when there were other recognisable cardiac abnormalities.

THALLIUM-201 SCINTIGRAPHY

Exercise and redistribution thallium-201 imaging was performed in 28 patients. There were fixed perfusion defects suggestive of myocardial scarring in four and reversible perfusion abnormalities were present in a further four patients (table 2).

ECHOCARDIOGRAPHY

Cross sectional and M mode echocardiography was attempted in all patients, but adequate scans for calculation of left ventricular mass could be obtained in only 25. In the remaining nine patients only qualitative assessment of the echocardiograms was possible. Valve abnormality was detected in only one patient (case 12), whose echocardiogram indicated the presence of a thickened, sclerotic aortic valve with mild stenosis. Left ventricular hypertrophy (wall thickness >11 mm) was detected in 12 (48%). In one patient (case 30) concentric left ventricular hypertrophy was associated with systolic anterior motion of the anterior mitral leaflet and calcification of the posterior mitral annulus but there were no other features to suggest hypertrophic cardiomyopathy. In another patient there was early systolic closure of the aortic valve (case 34).

There was no significant correlation between left ventricular wall thickness and peak filling rate ($r = 0{\cdot}1, p = \mathrm{NS}$ for septal thickness; and $r = 0{\cdot}3, p = \mathrm{NS}$ for posterior free wall thickness). The left ventricular cavity was dilated in five patients and of these two had other evidence of ischaemic heart disease. The remaining three had no evidence of hypertension or ischaemic heart disease. Increased left ventricular mass was detected in 17 (68%) of the patients by the criteria (>200 g) of Mather *et al.*[28] No significant correlation was detected between the left ventricular mass and peak filling rate ($r = -0{\cdot}3, p = \mathrm{NS}$).

RADIONUCLIDE VENTRICULOGRAPHY

Nineteen patients had no recognisable cause of heart disease. None was receiving any cardioactive medication at the time of study. The results of radionuclide ventriculography in these patients were analysed in detail and compared with the results from 22 age matched controls (table 3). None of these patients developed abnormalities of regional wall motion on exercise. Resting systolic function was similar in both the controls and the patients, but peak filling rates at rest were significantly depressed in the patients ($p < 0{\cdot}005$) despite comparable resting heart rates (fig 1). Mean exercise ejection fraction and ejection rate in the two groups were similar, but ejection time and time to peak filling rate were longer in the patients ($p < 0{\cdot}05$ and $p < 0{\cdot}02$ respectively). The significantly higher exercise heart rate in the controls than the patients ($p < 0{\cdot}01$) could account for this result. The diastolic indices remained abnormal on exercise in the patients. The change in mean ejection fraction on exercise was +4·1(8·4)% in the control group and +2·7 (10·0)% in the patients ($p = \mathrm{NS}$).

Table 2 *Results of exercise testing, echocardiography, thallium scintigraphy, and nuclear angiography*

Patient No	*Exercise time (min)*	*GXT result*	*GXT symptoms*	*Thallium scan*	*RNA WMA*	*LV mass (g)*
1	7 4	−	SOB	N	0	155
2	13 7	+	SOB	N	0	227
3	18·0	−	F	N	0	199
4	8 8	+	THR/F	N	0	291
5	8·4	−	SOB	N	0	243
6	6·3	−	SOB	N	0	214
7	17·9	−	THR/F	N/D	N/D	185
8	9 7	I/C	SOB/VE	R	+	−
9	13·4	−	THR/F	R	0	−
10	9·9	+	SOB	N	0	193
11	8 1	−	F	N	0	−
12	N/D	N/D	N/D	N	0	139
13	18·8	−	THR/F	N	0	−
14	14·0	−	F	N/D	N/D	228
15	15·7	−	F	N	0	333
16	14 0	+	SOB	N	0	207
17	17 9	−	F	N	0	258
18	18 0	−	F	N	0	287
19	12 3	−	SOB	N	0	261
20	15 0	−	F	N/D	0	261
21	10 8	−	F	N	0	−
22	2 9	−	SOB	Fx	+	−
23	2 1	I/C	SOB	N/D	N/D	−
24	20 0	−	THR/F	N/D	0	232
25	5·8	I/C	F	Fx	+	591
26	12·2	−	F	N	0	167
27	13 2	−	SOB	N	0	249
28	17·5	−	SOB	N/D	0	229
29	8·4	−	AP	R	+	−
30	1 0	I/C	SOB	R	0	186
31	19·6	−	F	Fx	0	353
32	4·1	−	SOB	Fx	0	361
33	18·7	+	F	N	0	160
34	9·5	I/C	SOB	N	0	−

WMA, wall motion abnormality; THR, target heart rate; SOB, shortness of breath; F, fatigue; I/C, inconclusive; R, reversible defect; Fx, fixed defect; N/D, not done; GXT, graded treadmill exercise test; AP, angina pectoris; N, normal angiography; VE, ventricular extrasystoles; RNA, radionuclide angiography.

RADIONUCLIDE VENTRICULOGRAPHY IN HYPERTENSIVE ACROMEGALIC PATIENTS

The results of radionuclide ventriculography in the nine hypertensive acromegalic patients were compared with those in normal age matched normotensive controls and with 14 age matched patients with essential hypertension (table 4). Five of the hypertensive acromegalic patients were receiving β blockers and one was on calcium antagonists at the time of study.

Resting ejection fraction was similar in the three groups, as were resting ejection rate and ejection time. Mean (SD) resting peak filling rate in the normal subjects was 2·9 (0·4) EDV/s. The essential

Table 3 *Results (mean (SD)) of radionuclide angiography in the 19 normotensive acromegalic patients and the 22 age matched controls*

	Controls	*Normotensive and aromegalic*	*Controls v acromegalics*
Rest variables:			
Ejection fraction (%)	61 (7)	61 (10)	NS
Ejection rate (EDV/s)	1·8 (0·3)	2·0 (0·5)	NS
Ejection time (ms)	350 (41)	330 (57)	NS
Peak filling rate (EDV/s)	2·9 (0·4)	2·4 (0·7)	<0·005
Early filling rate (EDV/s)	1·3 (0·4)	1·1 (0·5)	NS
Time to peak filling rate (ms)	161 (56)	193 (67)	NS
First one third filling fraction	0·5 (0·2)	0·4 (0·2)	NS
Heart rate (bpm)	69 (10)	72 (9)	NS
Exercise variables:			
Ejection fraction (%)	64 (9)	63 (9)	NS
Ejection rate (EDV/s)	2·8 (0·7)	2·4 (0·4)	NS
Ejection time (ms)	230 (46)	260 (30)	<0·05
Peak filling rate (EDV/s)	5·7 (1·2)	4·9 (1·7)	NS
Early filling rate (EDV/s)	2·7 (0·9)	2·5 (1·1)	NS
Time to peak filling rate (ms)	121 (32)	155 (53)	<0·02
First one third filling fraction	0·4 (0·2)	0·3 (0·1)	NS
Heart rate (bpm)	140 (24)	121 (16)	<0·01

EDV, end diastolic volume.

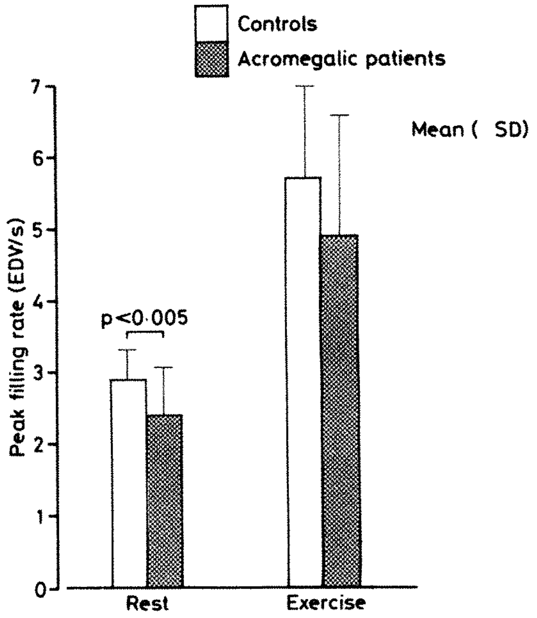

Fig 1 *Peak filling rate at rest and on exercise in normotensive patients with acromegaly and in age matched controls. EDV, end diastolic volumes.*

Table 4 *Results (mean (SD)) of radionuclide angiography in hypertensive acromegalic patients, patients with essential hypertension, and age-matched controls*

	Controls (n = 14)	*EHT (n = 14)*	*AHT (n = 9)*	*C v EHT*	*C v AHT*	*EHT v AHT*
Rest variables:						
Ejection fraction (%)	60 (6)	57 (8)	63 (9)	NS	NS	NS
Ejection rate (EDV/s)	1·8 (0·3)	1·9 (0·3)	2·0 (0·6)	NS	NS	NS
Ejection time (ms)	343 (46)	337 (54)	350 (77)	NS	NS	NS
Peak filling rate (EDV/s)	2·9 (0·4)	2·7 (0·8)	1·8 (0·5)	NS	<0·001	<0·01
Early filling rate (EDV/s)	1·4 (0·5)	0·2 (0·2)	0·9 (0·4)	<0·001	<0·02	<0·001
Time to peak filling rate (ms)	152 (53)	168 (41)	237 (87)	NS	<0·01	<0·05
First one third filling fraction	0·46 (0·25)	0·28 (0·17)	0·33 (0·17)	<0·05	NS	NS
Heart rate (bpm)	70 (11)	82 (16)	62 (12)	<0·05	NS	<0·01
Systolic blood pressure (mm Hg)	138 (16)	155 (21)	155 (25)	NS	NS	NS
Diastolic blood pressure (mm Hg)	85 (10)	102 (4)	94 (10)	<0·001	NS	NS
Age (yr)	54 (8)	52 (8)	56 (15)	NS	NS	NS
Exercise variables:						
Ejection fraction (%)	64 (9)	63 (8)	58 (14)	NS	NS	NS
Ejection rate (EDV/s)	2·6 (0·5)	2·7 (0·7)	2·0 (0·5)	NS	<0·05	<0·05
Ejection time (ms)	246 (43)	234 (40)	290 (80)	NS	NS	<0·05
Peak filling rate (EDV/s)	5·3 (1·3)	5·0 (1·1)	3·3 (1·0)	NS	<0·005	<0·005
Early filling rate (EDV/s)	2·6 (0·9)	2·2 (1·2)	1·4 (0·7)	NS	<0·01	NS
Time to peak filling rate (ms)	124 (34)	114 (34)	203 (59)	NS	<0·002	<0·001
First one third filling fraction	0·41 (0·16)	0·44 (0·23)	0·2 (0·12)	NS	<0·001	<0·02
Heart rate (bpm)	131 (21)	129 (19)	98 (19)	NS	<0·005	<0·005

EHT, essential hypertensives; AHT, hypertensive acromegalic patients; C, controls; EDV, end diastolic volume.

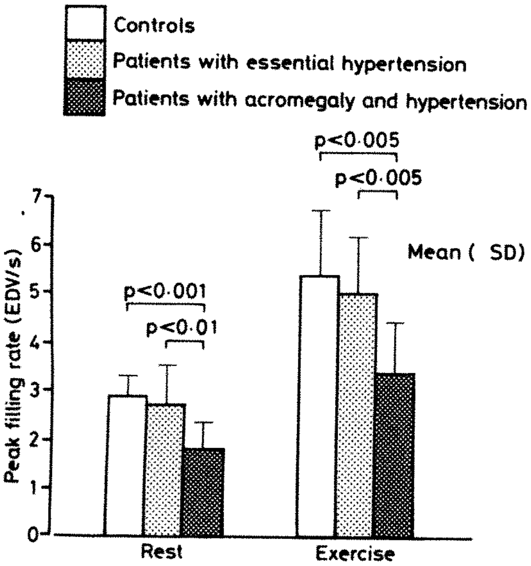

Fig 2 *Peak filling rate at rest and on exercise in hypertensive patients with acromegaly and in age-matched controls and patients with essential hypertension. EDV, end diastolic volumes.*

hypertension group had a slightly lower peak filling rate (2·7(0·8) EDV/s, $p = NS$) but in the hypertensive acromegalic patients the peak filling rate was significantly depressed (1·8(0·5) EDV/s, $p < 0·001$) (fig 2). A similar abnormality was seen in time to peak filling rate. The first one third filling fraction was abnormal in the patients with essential hypertension but not in those with acromegaly and hypertension. The early filling rate was lower in both hypertensive groups than in the controls.

COMPARISON BETWEEN ACTIVE AND TREATED ACROMEGALY

Of the acromegalic patients studied, seven had raised (> 10 mU/l) serum concentrations of growth hormone at the time of study. The results of radionuclide ventriculography in this group were compared with results from 13 patients whose growth hormone concentrations were well within the normal range (< 10 mU/l) at the time of the study. No significant difference in either systolic or diastolic function was detected between these groups although resting peak filling rate was slightly lower in patients with active disease (2·0(0·9) EDV/s) than in treated patients (2·2(0·8) EDV/s) $p = NS$).

Discussion

Cardiac hypertrophy, "cardiomyopathy", and congestive cardiac failure have been described in as many as one third of patients with acromegaly[2-4] but the pathophysiology of cardiac dysfunction in this condition remains unclear.[7 9] In this study there was evidence of hypertension in 26% of patients, which accords with other reported series, as did the frequency of ischaemic heart disease.[6 29] Cardiac dysfunction in acromegaly has been attributed to these known causes of heart disease.[9] No previous study, however, has excluded coronary artery disease and hypertension from the study population. We have attempted to do this using a combination of electrocardiography, exercise testing, and stress thallium-201 scintigraphy.

Using electrocardiography alone, we detected left ventricular hypertrophy by Romhilt and Estes's criteria[27] in only three (9%) of our patients. But electrocardiography has limitations for detecting ventricular hypertrophy in these patients, because acromegaly results in a considerable alteration in the shape of the chest wall with an increase in anteroposterior diameter and hence greater than normal electrical insulation of the heart from surface electrodes. When it is technically feasible, echocardiography overcomes these difficulties and in this study there was evidence of left ventricular hypertrophy in 48% and an increased left ventricular mass in 68%. Similar results were reported by others.[28]

In five (15%) the exercise test was positive by ST segment criteria but in all of them thallium-201 scintigraphy was normal. A previous study from our department showed that positive exercise tests in patients with left ventricular hypertrophy are inaccurate predictors of coronary artery disease unless thallium-201 scintigraphy is also abnormal.[30] Quantitative thallium-201 imaging is well established and has been shown to be a highly sensitive technique for detecting underlying coronary artery disease.[19 31] Harris *et al* have also reported false positive exercise tests in patients with left ventricular hypertrophy and angiographically normal coronary arteries.[32] Because angina or wall motion abnormalities did not develop in any of these acromegalic patients during exercise radionuclide angiography, these positive exercise test results in conjunction with negative thallium-201 scans make it unlikely that obstructive disease was present in the large coronary arteries.

Cardiovascular morbidity is more common in acromegaly.[29] While cardiac failure may be responsible for this, some workers reported an increased incidence of arrhythmias in these patients.[5] In our series, 14 of the 34 patients had arrhythmias. One patient had several episodes of symptomatic ventricular tachycardia, but this patient undoubtedly had ischaemic heart disease and this was probably the cause of the arrhythmia. Thirteen patients had frequent ventricular extrasystoles and in one patient there were long periods of asymptomatic ventricular bigeminy. Arrhythmia was also more in patients with left ventricular hypertrophy and strain in the presence of normal coronary arteries,[33] a finding that may also be applicable to acromegalic patients.

Others have used systolic time intervals to study patients with acromegaly, with conflicting results. Jonas *et al* studied 10 patients and showed an abnormally high PEP/LVET (pre-ejection phase/left ventricular ejection time) ratio in six[7]—but five patients had hypertension, one had thyrotoxicosis, and one had diabetes mellitus. Furthermore, coronary heart disease was excluded by history and physical examination alone, without exercise testing or thallium-201 scintigraphy. Because it is well recognised that an increased PEP/LVET ratio may occur in patients with congestive cardiac failure, hypertension, and various myocardial diseases, the demonstration of an abnormality in this group of patients does not necessarily imply that impaired systolic function was caused by acromegaly. Martins *et al* studied 16 patients and found an abnormally high PEP/LVET in three with concomitant angina or hypertension.[8] Only one other patient, in whom coronary artery disease and hypertension had been excluded, showed abnormal systolic time intervals. Similarly, four of the 23 patients studied by Mather *et al* had high PEP/LVET ratios.[28] In three of these, causes other than acromegaly were clearly implicated. Our findings accord with those of Martins *et al*[8] and Mather *et al*[28] because an abnormal PEP/LVET ratio was only detected in patients with coexisting coronary heart disease. Systolic time intervals, however, are not as sensitive or specific as radionuclide angiography for assessing cardiac function[34] and it is therefore unlikely that subtle subclinical cardiac dysfunction would be detected by this method.

Most workers used echocardiography for assessing left ventricular function.[28 35 36] This technique is insensitive because of the assumptions necessary to calculate ejection fraction.[37] Furthermore, any errors in measuring wall thickness and cavity size are exaggerated when these values are used to derive volumes. It is now generally accepted that radionuclide angiography is a more accurate method of assessing left ventricular function. In two previous studies, patients with acromegaly were investigated by radionuclide angiography,[8 9] and in neither was cardiac dysfunction shown unless coexisting hypertension or ischaemic heart disease was present. Only left ventricular ejection fraction (systolic function) was measured, however. Our results accord with these studies in that we were unable to detect any abnormality of systolic function in acromegalic patients who had no evidence of other cardiac disease.

Left ventricular diastolic function has not previously been studied in acromegaly. Several workers have suggested that diastolic filling is more sensitive than ejection fraction for assessing early impairment of cardiac function, not only in ischaemic heart disease[10 11] but also in other conditions such as hypertrophic cardiomyopathy[15] and hypertension.[14] In our study there was a highly significant difference in resting peak filling rate between controls and patients with acromegaly. The diastolic peak filling rate was reduced and the time to peak filling rate was prolonged, indicating impaired diastolic relaxation. Diastolic indices remained abnormal on exercise. This abnormality of diastolic filling was apparent even in those acromegalic patients in whom hypertension and ischaemic heart disease were excluded.

Altered diastolic relaxation may be caused by abnormalities in the active energy-dependent relaxation process as is the case in patients with acute myocardial ischaemia,[10-12] or by an increase in the visco-elastic properties of the left ventricle as occurs after myocardial infarction.[38 39] While the increased left ventricular mass seen in acromegaly may reduce compliance, this factor is unlikely to be solely responsible for our findings, because there was no correlation between diastolic filling variables and left ventricular wall thickness or left ventricular mass. Lie and Grossman showed mononuclear cell infiltrate or myocarditis in up to 59% of cases of acromegaly.[6] Hejmancik *et al* also reported increased interstitial fibrosis in acromegaly.[3] It is not known whether the finding of an inflammatory reaction relates to the activity of the acromegaly with fibrosis representing "healing" once the condition is treated. Although we found no difference in diastolic dysfunction between active and treated acromegaly, the reduced peak filling rate detected in our study may well reflect these histological abnormalities, which would be expected to increase ventricular stiffness and reduce compliance. Our study therefore adds clinical support to the necropsy evidence for a specific heart muscle disease in acromegaly.

Furthermore, acromegalic patients with coexistent hypertension showed greater depression of diastolic function than age and blood pressure matched patients with essential hypertension, suggesting that hypertension may be less well tolerated when there are underlying acromegalic changes in the myocardium; this factor may contribute to the increased frequency of clinical cardiac disease in acromegaly. Some of the hypertensive acromegalic patients in our study, however, were receiving β blockers and abnormalities of peak filling rate may have been exaggerated by the negative chronotropic properties of these agents. Early therapeutic intervention with addition of calcium antagonists may improve the diastolic abnormalities detected.[15 40]

We found evidence of subclinical cardiac dysfunction in acromegaly in the absence of other known causes of heart disease and our findings are consistent with the histological abnormalities previously shown in the hearts of patients with acromegaly.

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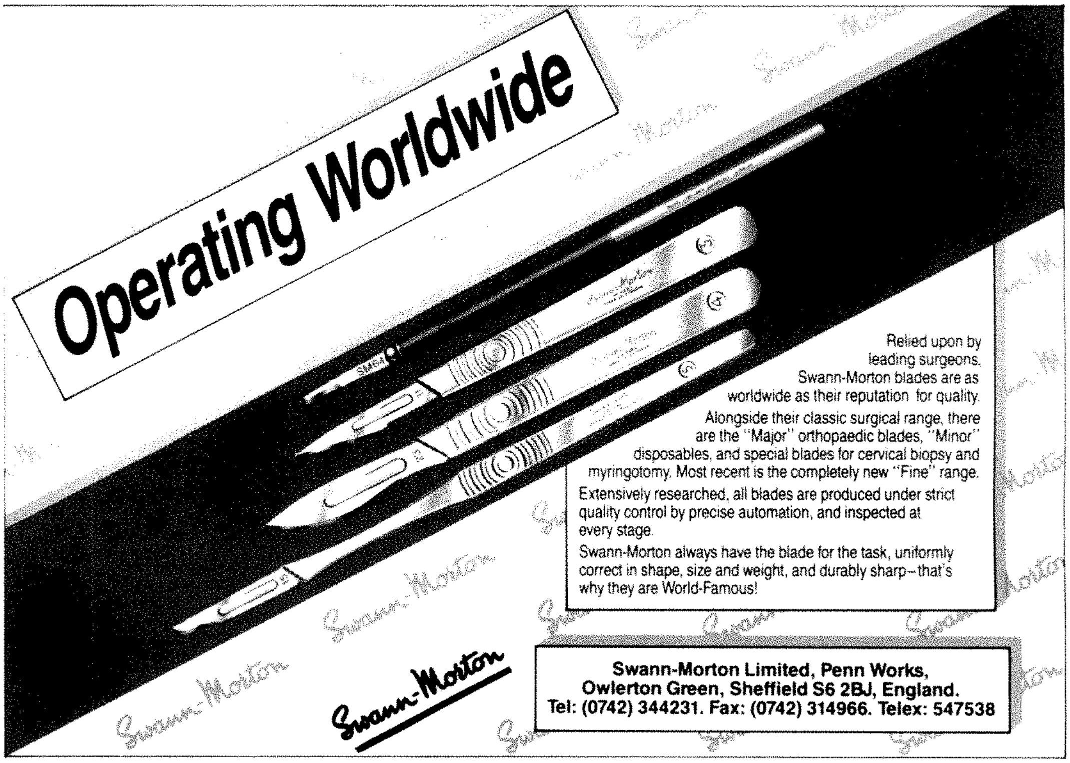

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Value and limitations of adenosine in the diagnosis and treatment of narrow and broad complex tachycardias

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SUMMARY The diagnostic and therapeutic potential of intravenous adenosine was studied in 64 patients during 92 episodes of regular sustained tachycardia. In 40 patients who had narrow complex tachycardias (QRS $<0{\cdot}12$ s) adenosine (2·5–25 mg) restored sinus rhythm in 25 with junctional tachycardias (46 of 48 episodes) and produced atrioventricular block to reveal atrial or sinus tachycardia in 15. In 24 patients with broad complex tachycardias (QRS $\geqslant 0{\cdot}12$ s) adenosine terminated the tachycardias in six patients and revealed atrial or sinus arrhythmias in four. The tachycardias persisted in 14 patients despite doses up to 20 mg, but adenosine allowed the diagnosis of ventricular tachycardia with retrograde atrial activation in two patients by producing transient ventriculoatrial dissociation. Diagnosis based on adenosine induced atrioventricular nodal block was correct in all patients with narrow complex tachycardias and in 92% of those with broad complex tachycardias, compared with correct electrocardiographic diagnoses in 90% and 75% respectively. Adenosine gave diagnostic information additional to the electrocardiogram in 25%. The response to adenosine in broad complex tachycardias identified those of supraventricular origin with 90% sensitivity, 93% specificity, and 92% predictive accuracy. Adenosine restored sinus rhythm in all patients with junctional reentrant tachycardias, but in 10 (35%) the arrhythmias recurred within two minutes. Symptomatic side effects (dyspnoea, chest pain, flushing, headache) were reported by 40 (63%) patients and, although transient, were severe in 23 (36%). There were ventricular pauses of over 2 s in 16% of patients, the longest pause being 6·1 s.

Adenosine is of value in the diagnosis and treatment of narrow and broad complex tachycardias, but its use is limited by symptomatic side effects, a tenfold range in minimal effective dosage, occasional action at sites other than the atrioventricular node, and early recurrence of arrhythmia.

Adenosine is a naturally occurring, rapidly metabolised compound that produces transient atrioventricular nodal block in humans when injected intravenously.[1] It can terminate reentrant supraventricular tachycardias that involve the atrioventricular node,[2-4] while in tachycardias of atrial origin it may be of diagnostic value, because adenosine induced atrioventricular block slows the ventricular rate and reveals the unaffected atrial arrhythmia.[2] Such diagnostic and therapeutic effects of adenosine should be of most value in broad complex tachycardias (which are often misdiagnosed[5]) by acting on supraventricular tachycardias with aberrant conduction, while having no effect on ventricular tachycardia.[6] The brief duration of action of adenosine is of particular advantage in this context, making it a safer alternative to verapamil.[7] The diagnostic use of adenosine based on its property of blocking the atrioventricular node may be questioned, however, because adenyl compounds can also act on accessory pathways,[8 9] and may terminate some atrial[10] and ventricular[11] tachycardias. We therefore studied the clinical value of adenosine in patients with regular narrow or broad complex tachycardias to determine whether it provides diagnostic information additional to the surface electrocardiogram and to assess its therapeutic value.

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Patients and methods

Adenosine was administered to 64 patients (36 men and 28 women, aged 16–79 years (mean 51 years)), during 92 episodes of sustained regular tachycardia. Fifty four patients were studied during spontaneous episodes of tachycardia, on 75 occasions, while in 15 patients the tachycardias were induced by programmed stimulation; five patients received adenosine during both spontaneous and induced tachycardias. Electrocardiographic diagnoses were based on standard criteria for narrow[12 13] and broad[14] complex tachycardias. Electrophysiological studies, with standard protocols,[15] confirmed the diagnoses in 27 patients.

An adenosine (Sigma) solution (5 mg/ml) was prepared in sterile saline. Boluses of 2·5–25 mg were administered by rapid intravenous injection via arm veins in most patients or into femoral or central veins in 16 patients. The dose was increased, to a maximum of 20 mg, by 2·5 or 5 mg after the effects of the preceding dose had passed, until there was an effect on the arrhythmia or the patient reported intolerable side effects. One patient with recurrent supraventricular tachycardia required an additional 25 mg bolus to terminate the arrhythmia. A continuous electrocardiogram was recorded during and for a minute after the administration of each dose. Blood pressure was measured by cuff sphygmomanometer or by intra-aortic pressure recording in patients undergoing electrophysiological study. Side effects were assessed by direct questioning and were scored by the patient from 0 to 10 ("very mild" to "very severe").

When the diagnostic value of adenosine was assessed it was assumed that it had its main action on the atrioventricular node and thus (*a*) reentrant junctional tachycardias would be terminated, (*b*) atrial and sinus tachycardia would persist and be exposed when the ventricular rate was slowed by atrioventricular block, and (*c*) ventricular tachycardia would be unaffected. The mode of termination of junctional tachycardias was examined to determine the site of action of adenosine within the reentrant circuit. The post-tachycardia sinus beats were examined for pre-excitation, because conduction down an accessory pathway may be enhanced by adenosine induced atrioventricular block. The diagnostic yield from the responses to adenosine was compared with the electrocardiographic diagnoses and the results of electrophysiological study.

Results were expressed as means and standard deviations and the *t* test was used to test for differences between means.

Results

NARROW COMPLEX TACHYCARDIAS

Forty patients with narrow complex tachycardias received adenosine during 64 episodes—55 spontaneous and nine induced at electrophysiological study. The QRS duration ranged from 0·04 to 0·08 s (mean 0·07 s) and the tachycardia rates from 120 to 240 beats/min (mean 170 beats/min). Adenosine produced an effect in all patients with narrow complex tachycardias, restoring sinus rhythm in 25 patients (46 of 48 episodes) (fig 1) and producing atrioventricular block to reveal atrial or sinus

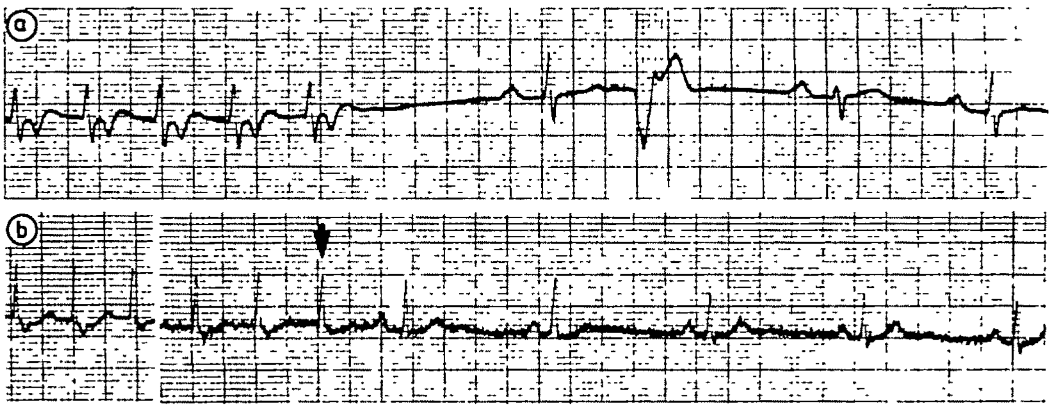

Fig 1 *Termination of junctional tachycardias by adenosine. (a) In a patient with a concealed accessory pathway the tachycardia terminated 20 seconds after administration of 20 mg adenosine. Adenosine blocked the anterograde limb of the reentrant circuit as retrograde atrial activation followed the last QRS complex of the tachycardia.*
(b) Termination of junctional tachycardia by 20 mg adenosine in a patient with dual atrioventricular nodal pathways. The retrograde atrial activation seen during the tachycardia is absent after the last QRS complex of the tachycardia (arrowed) indicating block of the retrograde limb of the reentrant circuit. The initial three complexes are from tracings before adenosine. Somatic tremor artefact associated with adenosine induced symptoms. Paper speed 25 mm/s.

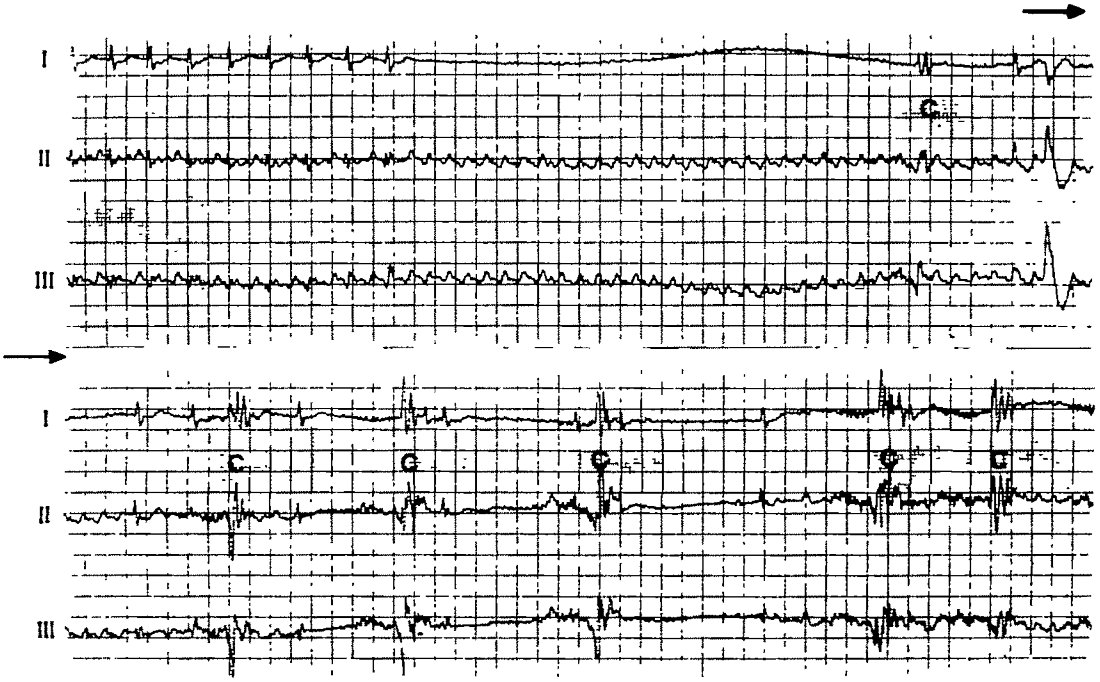

Fig 2 *Continuous tracings in leads I, II, and III showing atrioventricular block and transient termination of atrial flutter by adenosine. Five seconds after adenosine administration atrioventricular block revealed flutter waves and resulted in ventricular standstill for 6·1 s. There were artefacts caused by coughs (C). Thirteen seconds after adenosine administration atrial flutter was terminated (bottom panel) but atrial flutter/fibrillation recurred. Paper speed 25 mm/s.*

tachycardias in 15 patients (fig 2). The time to onset of the action of adenosine ranged from 5 to 40 s after intravenous injection (mean (SD) 19·5 (8·3) s). The duration of effect in patients with atrial tachycardias was dose dependent, with atrioventricular block persisting for 6–30 s (mean 13 s). There was a tenfold range in the minimum effective dose of adenosine, from 2·5 to 25 mg, with a mean (SD) dose of 8·8 (6·2) mg. The dose varied between individuals but also depended on the route of administration. The mean (SD) dose to terminate the tachycardias was 3·0 (1·1) mg ($n = 10$) when administered via the femoral vein and 10·8 (6·3) mg ($n = 36$) via peripheral veins ($p < 0·001$).

An electrocardiographic diagnosis of probable junctional tachycardia was made in 24 patients with narrow complex tachycardias. Adenosine terminated the tachycardias in 22 of these patients, but revealed atrial tachycardia with first degree atrioventricular block in one and atrial flutter with 1:1 conduction in another. Five patients had tachycardias with P waves preceding each QRS complex. Adenosine induced atrioventricular block confirmed sinus or atrial tachycardia in two with superior to inferior P wave axes and terminated the tachycardia in the remaining three. Atrial flutter with 2:1 block was diagnosed from the electrocardiogram in 11 patients, and in each of these adenosine slowed the ventricular rate to reveal atrial flutter waves. Adenosine briefly terminated atrial flutter in one patient (fig 2).

Termination of junctional tachycardias by adenosine was the result of a block of the atrioventricular node in most patients, including 11 with accessory pathways (fig 1a). In four patients adenosine blocked the retrograde limb of the reentrant circuit, the last activity of the tachycardia being ventricular (fig 1b). This need not necessarily indicate an atrioventricular nodal tachycardia, as was shown by the patient in fig 3. Adenosine caused prolongation of the AH interval but the tachycardia was terminated by a block of retrograde conduction in what proved to be a concealed paraseptal accessory pathway of the less common slowly conducting type. An underlying diagnosis of Wolff-Parkinson-White syndrome was revealed by the response to adenosine in six patients, because the transient atrioventricular block enhanced pre-excitation owing to conduction down an accessory pathway (fig 4).

BROAD COMPLEX TACHYCARDIAS

Twenty four patients with broad complex tachycardias received adenosine during 28 episodes—20

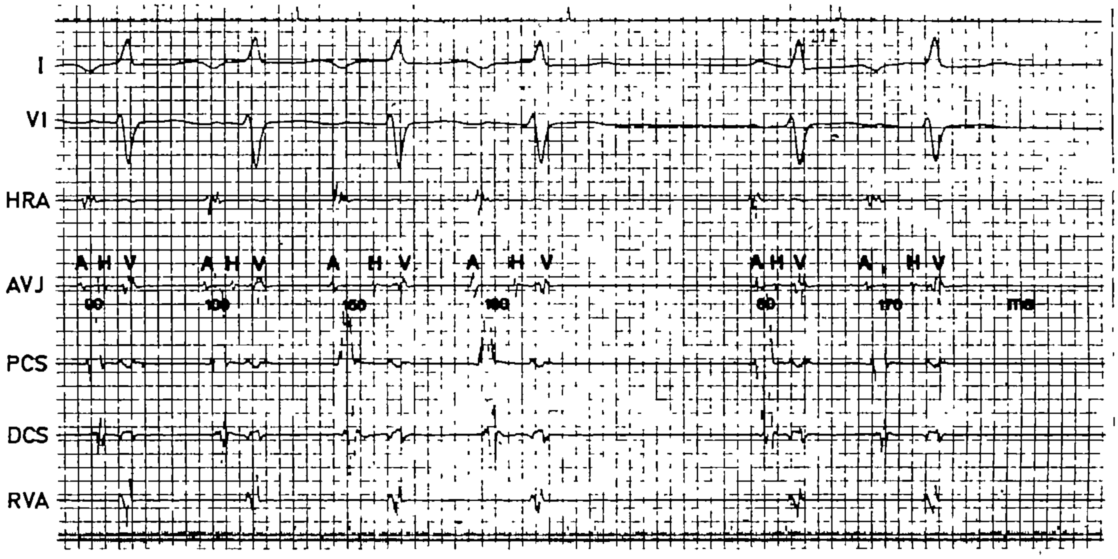

Fig 3 *Termination of long RP junctional tachycardia by adenosine induced retrograde block. Twenty seconds after 2·5 mg adenosine administration there was prolongation of the AH interval, but block then occurred retrogradely, after ventricular activation, as adenosine blocked conduction in a slowly conducting concealed paraseptal accessory pathway. After the post-tachycardia pause, both atrioventricular nodal and accessory pathway function recovered for the first sinus beat but the persisting adenosine effect produced AH prolongation and accessory pathway block with the subsequent reentrant beat. Surface leads I and V1. Intracardiac electrograms from high right atrium (HRA), atrioventricular junction (AVJ), proximal coronary sinus (PCS), distal coronary sinus (DCS), and right ventricular apex (RVA). Paper speed 100 mm/s.*

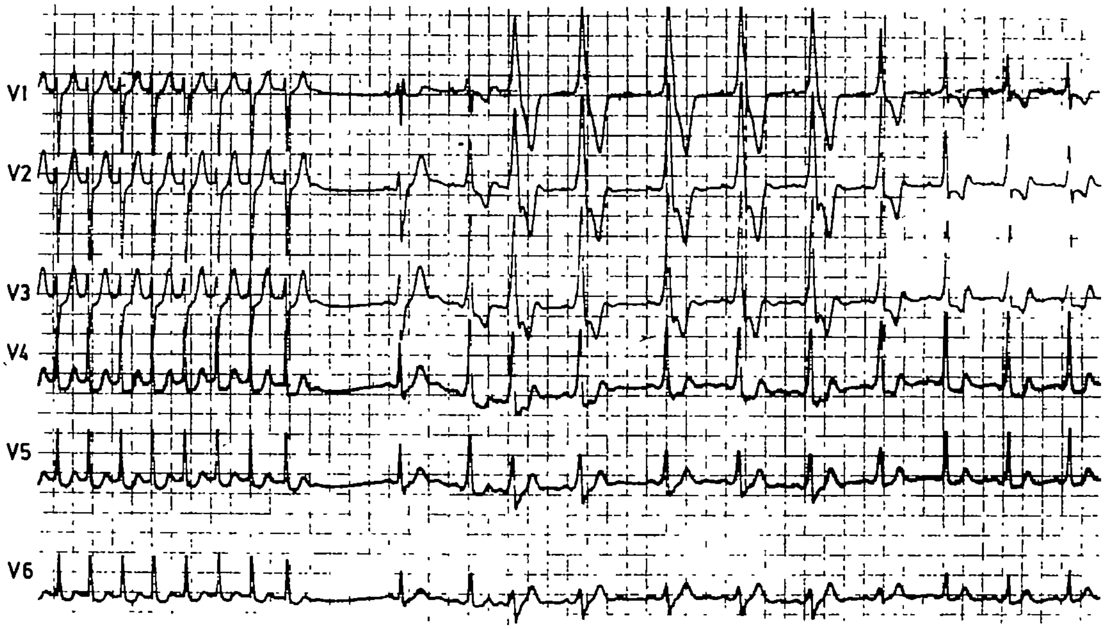

Fig 4 *Pre-excitation after termination of junctional tachycardia by adenosine (2·5 mg) as transient atrioventricular block produced relative enhancement of conduction down a left sided accessory pathway. The first sinus beat was not overtly pre-excited, which may indicate transient block of accessory pathway conduction or may reflect delay in the onset of progressive atrioventricular nodal block. Chest leads V1–V6. Paper speed 25 mm/s.*

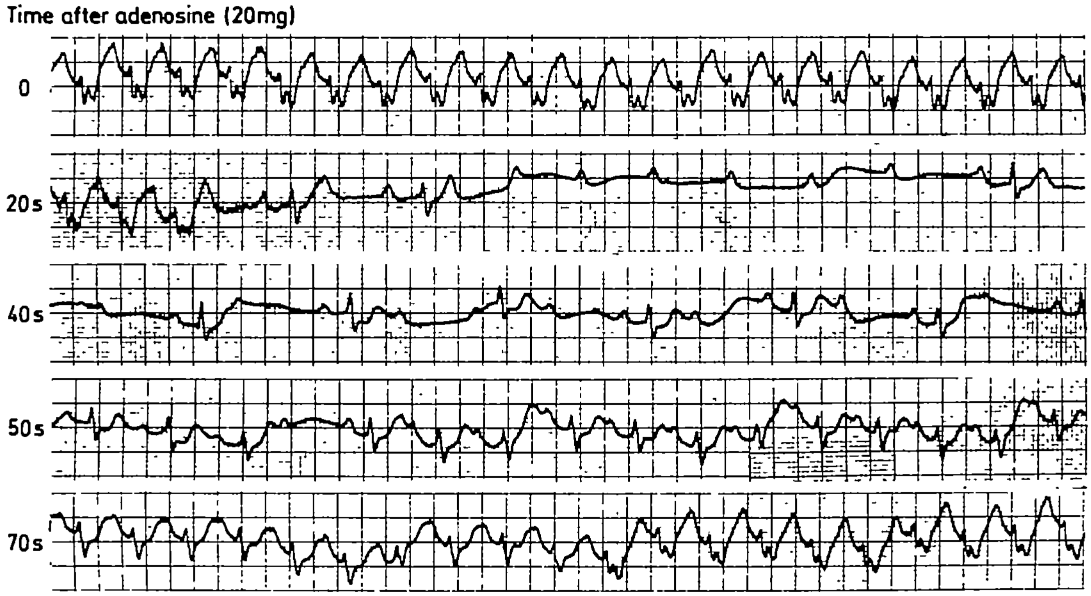

Fig 5 *Broad complex tachycardia revealed as sinus tachycardia by adenosine. An arrhythmia with a configuration that was suggestive of ventricular tachycardia was terminated by the onset of atrioventricular block, with 5 s ventricular standstill, 20 s after administration of 20 mg adenosine. The atrial rate then increased and atrioventricular conduction returned as the adenosine effect passed, with second degree block by 40 s, first degree by 50 s, and sinus tachycardia by 60 s. At 70 s the rate was the same as before adenosine, but the complexes were narrow, until they became aberrant again at 80 s (middle lower panel). Lead II, paper speed 25 mm/s.*

spontaneous and eight induced. The mean (SD) QRS duration was 0·14 (0·03) s and the tachycardia rates ranged from 110 to 240 beats/min (mean 162 beats/min). Adenosine terminated the tachycardias in six patients (eight of nine episodes) and induced atrioventricular block to reveal atrial or sinus tachycardias in four patients. As with narrow complex tachycardias, there was a wide range of minimum effective dosage, from 2·5 to 20 mg (mean (SD) 11·0 (5·6) mg). The tachycardias persisted despite doses of 10 to 20 mg intravenous adenosine (mean (SD) 17·7 (4·2) mg) in the remaining 14 patients.

The patients with broad complex tachycardia were divided into two groups according to the relation between atrial and ventricular activity on the electrocardiogram. Atrioventricular dissociation was not apparent in 13 patients. Adenosine restored sinus rhythm in five patients in whom the electrocardiogram indicated junctional tachycardia with aberrant conduction and revealed unsuspected atrial flutter in two patients and sinus or atrial tachycardia in two (fig 5). Tachycardia persisted despite the administration of 20 mg of adenosine in four patients, suggesting the diagnosis of ventricular tachycardia. This was confirmed in two patients, who had atrial activity after each QRS complex, by adenosine induced block of retrograde conduction and the production of ventriculoatrial dissociation (fig 6). Evidence of atrioventricular dissociation was present in the remaining 11 patients, suggesting ventricular tachycardia. Adenosine had no effect on the tachycardia in 10 of these patients, but in one the tachycardia briefly accelerated and then terminated in the first minute after adenosine administration. After the reinduction of the tachycardia, repeat administration of adenosine up to 20 mg failed to terminate the arrhythmia.

CLINICAL VALUE AND LIMITATIONS OF ADENOSINE

The response to adenosine gave the correct basic diagnosis in all patients with narrow complex tachycardia and in 92% of those with broad complex tachycardia (table), while the electrocardiographic diagnosis was correct in 90% of narrow complex tachycardias and 75% of broad complex tachycardias. Adenosine gave diagnostic information additional to the electrocardiogram in 16 patients (25%). In patients with broad complex tachycardias, adenosine produced atrioventricular block and terminated or revealed tachycardias of supraventricular origin, with a sensitivity of 90%, specificity of 93%, and predictive accuracy of 92%.

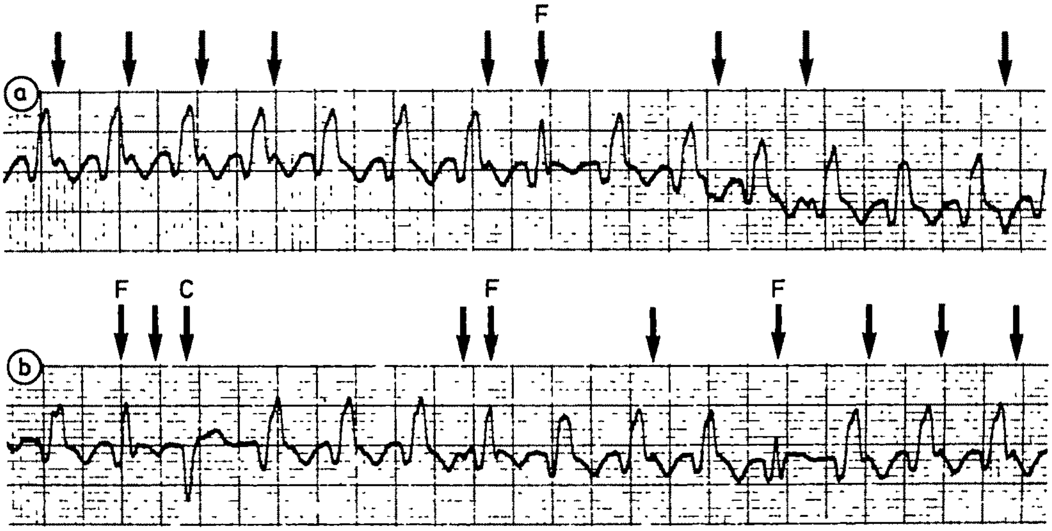

Fig 6 *Adenosine induced ventriculoatrial block in a patient with ventricular tachycardia and 1:1 retrograde conduction (a) 30 s and (b) 45 s after adenosine (10 mg). The response to adenosine showed that the small notch following the first four QRS complexes was caused by atrial activity (unlabelled arrows), because it disappeared with the onset of atrioventricular block and the loss of retrograde ventriculoatrial conduction. The resultant dissociated atrial activity produced fusion beats (F) (with narrowed QRS complexes) and a capture beat (C) (with a configuration identical with that seen on return to sinus rhythm) before the recurrence of retrograde conduction (last three complexes). Lead V1, paper speed 25 mm/s.*

Adenosine effectively restored sinus rhythm in all 29 patients with junctional reentrant tachycardias. However, the arrhythmia recurred within two minutes (mean 35 s) of the restoration of sinus rhythm in 10 (35%) of these patients (19 of 26 episodes). Electrocardiograms, obtained in 12 episodes, showed re-initiation of tachycardia by atrial extrasystoles in four patients, by ventricular extrasystoles in two, and by retrograde activation of the atria without preceding extrasystoles in three patients (fig 7). Five patients had sinus tachycardias (100 to 130 beats/min) when their tachycardias were re-initiated by atrial or ventricular extrasystoles at a mean interval of 50 s after termination. By contrast, in four episodes when the arrhythmias were re-initiated by retrograde atrial activation without preceding extrasystoles, recurrence was earlier, at 6 to 15 s (mean 9 s), and the mean heart rate was 46 beats/minute.

The negative chronotropic and dromotropic actions of adenosine may result in pronounced bradycardia if an excessive dose is administered (figs 2 and 5), but this did not occur in most patients. After termination of junctional tachycardias by adenosine, short pauses of up to 2·46 s occurred (mean ventricular pause 1·28 s). More pronounced bradycardias were seen in patients with atrial or sinus arrhythmias in whom larger doses of adenosine induced atrioventricular block with ventricular pauses of up to 6·1 s (mean pause 1·9 s). Ventricular pauses of more than 2 s occurred in 10 (16%) patients. The recovery of heart rate was always rapid and the bradycardia was usually followed by sinus tachycardia.

Ventricular extrasystoles occurred in response to adenosine in 20 (44%) of the 46 patients with supraventricular arrhythmias. Single ventricular

Table *Diagnostic value of the electrocardiogram and responses to adenosine*

Arrhythmias	*Junctional tachycardia*	*Atrial flutter*	*Atrial or sinus tachycardia*	*Ventricular tachycardia*
Narrow complex:				
ECG	23/25	11/12	2/3	—
Adenosine	25/25	12/12	3/3	—
Broad complex:				
ECG	4/5	0/2	2/3	12/14
Adenosine	5/5	2/2	2/3	13/14

Figures show the number of patients correctly diagnosed and the total number of patients with the diagnosis. See text for diagnostic criteria.

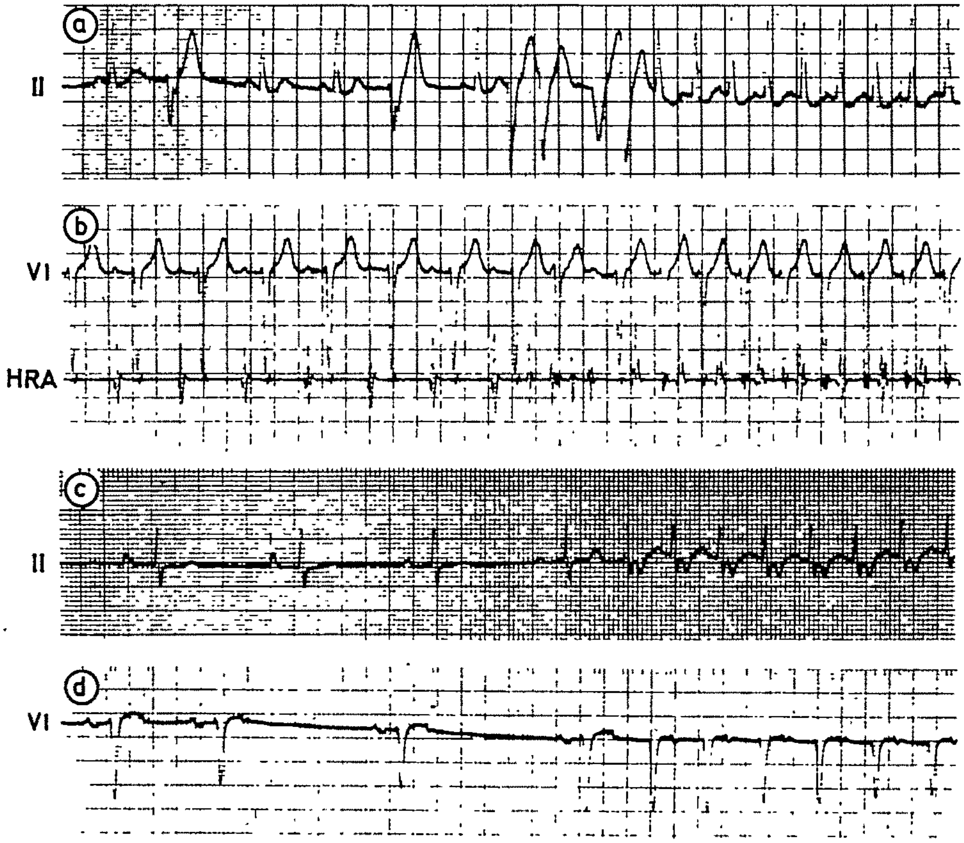

Fig 7 *Early recurrence of junctional tachycardia after termination by adenosine. (a) Twenty seconds after restoration of sinus rhythm by 7·5 mg adenosine a junctional tachycardia was re-initiated by ventricular extrasystoles. (b) Re-initiation of junctional tachycardia by multiple atrial extrasystoles in a patient with sinus tachycardia 30 s after restoration of sinus rhythm by 5 mg adenosine. (c) Forty seconds after termination of junctional tachycardia by adenosine 7·5 mg a single atrial extrasystole caused a further increase in PR interval and re-initiated the tachycardia in a patient with resting sinus bradycardia and first degree heart block. (d) Ten seconds after restoration of sinus rhythm by 5 mg adenosine retrograde atrial activation was seen after the sinus beats, and the third such beat re-initiated the tachycardia. Note the identical configuration of retrograde atrial beats before and after reinduction of tachycardia. Leads II or V1. HRA, high right atrial electrogram. Paper speed 25 mm/s.*

extrasystoles occurred in nine patients, ventricular couplets in seven, and short episodes of non-sustained ventricular tachycardia in four. No persisting adverse effect resulted from these arrhythmogenic effects of adenosine, other than the involvement of ventricular extrasystoles in the re-initiation of junctional tachycardia in two patients (fig 7).

Symptomatic side effects were reported after adenosine was administered to 40 (64%) of the patients. These included dyspnoea (36%), chest pain (31%), flushing (21%), and headache (12%). Symptoms were of similar short duration to the cardiac effects and had passed by one minute. Twenty three patients, however, described symptoms of more than moderate severity (scores of over 5/10), and 11 of them felt that the side effects were severe (scores of 8–10/10). Eighteen (29%) reported multiple symptoms. No adverse haemodynamic response was seen in any of the patients including the six patients being treated with β blockers. There was no change in the measured blood pressure other than increases after restoration of sinus rhythm.

Discussion

The negative dromotropic action of intravenous adenosine in humans was first described in 1930 by Honey *et al*, but they concluded that they did "not regard adenosine as a useful therapeutic preparation for the treatment of heart disease".[16] But the present results confirm more recent conclusions that adenosine is useful.[2-4] The diagnostic and therapeutic effects of adenosine are attributable to its negative dromotropic action, mediated by a direct action on specific purine receptors in the heart.[17] Its actions are not antagonised by atropine, but are blocked by aminophylline,[1] and are probably caused by receptor mediated increases in potassium conductance,[18 19] with hyperpolarisation of the nodal cells.[20] Side effects may also be the result of stimulation of specific purine receptors, with chest pain mediated by adenosine sensitive pain receptors,[21] and stimulation of respiration secondary to an action on the carotid body.[22] The rapid metabolism of adenosine in blood, with a half life in the circulation of about 10 s,[23] limits its use to the short term management of paroxysmal arrhythmias.

Although expert interpretation of the electrocardiogram will provide the correct diagnosis in most patients with tachycardias,[13-15] it is recognised that such expertise is often not available. Many tachycardias, particularly those with broad complexes, are misdiagnosed.[5] This may have serious therapeutic implications, because verapamil has been commonly administered to patients with ventricular tachycardia misdiagnosed as supraventricular with aberration.[7] While the response to verapamil may also be of diagnostic value,[24] the high incidence of adverse effects makes its use inadvisable.[7 25 26] By contrast, the use of adenosine in the acute diagnosis and treatment of broad complex tachycardias seems to be safe. Adenosine has been reported to have a similar diagnostic value in regular broad complex tachycardias initiated by programmed stimulation, when the diagnosis of ventricular tachycardia is based solely on the lack of an effect of adenosine.[6] The present results additionally show that adenosine may allow a positive diagnosis of ventricular tachycardia in those patients with 1:1 retrograde atrial activation, by producing ventriculoatrial dissociation.

The responses to adenosine in patients with narrow complex tachycardias allowed correct diagnosis in the few in whom the electrocardiogram had been misleading, and also indicated a possible anatomical basis for junctional tachycardias by showing pre-excitation in sinus rhythm. Tachycardia may be terminated by retrograde block in atrioventricular nodal tachycardias,[2] but it cannot be considered as diagnostic of a nodal basis to the arrhythmia because accessory pathways may also be blocked by adenosine and other adenyl compounds.[8 9] The termination of atrial flutter by adenosine might also be misleading, particularly in the absence of prior atrioventricular block, as may occur with conduction down an accessory pathway.[6] Similarly, transient termination of atrial tachycardia by adenosine triphosphate has been reported,[10] emphasising that termination of arrhythmia by adenyl compounds is not completely specific for junctional tachycardia. The termination of ventricular tachycardia after adenosine in our patient was probably not a direct action of adenosine, but secondary to the positive chronotropic influences that commonly follow the negative effects of adenosine.[27 28] Adenosine, however, has been shown to terminate reproducibly catecholamine or exercise induced ventricular tachycardia that is thought to be due to triggered activity mediated by cyclic adenosine monophosphate in patients with normal hearts.[6 11] Thus termination of arrhythmia by adenosine is neither completely diagnostic of junctional tachycardia, nor even of a tachycardia of supraventricular origin.

Adenosine restored sinus rhythm in all patients with junctional tachycardias, but arrhythmia quickly recurred in a third of them. This seems to be attributable to more than the short duration of action and lack of persisting antiarrhythmic effect. Adenosine induced bradycardia is followed by tachycardia, presumably mediated by the sympathetic nervous system, possibly owing to carotid body stimulation by adenosine,[22 28] and catecholamine induced extrasystoles which may have triggered the tachycardias. Earlier recurrences, during the bradycardiac phase of adenosine, may have resulted from a critical degree of atrioventricular delay occurring as the action of adenosine passed, the slowed anterograde conduction allowing recovery of the retrograde pathway and subsequent atrial activation. The high rate of recurrence may reflect the patient population, as some of these patients had troublesome recurrent arrhythmias, and such a high recurrence rate has not been reported before.[2-4] In two of these patients with recurrence after adenosine, however, the tachycardias could be terminated by atrial pacing without early recurrence of arrhythmia, suggesting that adenosine may have been provoking re-initiation.

Adenosine is effective in the diagnosis and treatment of both narrow and broad complex tachycardias. Its value is limited by occasional action at sites other than the atrioventricular node and early recurrence of junctional tachycardia after restoration of sinus rhythm. The dose must be increased cautiously because of the high incidence of transient but occasionally severe side effects and the wide range of minimal effective dosage. An important clinical application of adenosine is in broad complex tachycardias in patients in whom the diagnosis is in doubt. Adenosine provides a safe means of diagnosis and treatment in such patients.

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Efficacy and safety of adenosine in the treatment of supraventricular tachycardia in infants and children

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SUMMARY One hundred and seventeen episodes of supraventricular tachycardia in 50 children, including 28 infants, were treated with intravenous adenosine. Adenosine was prepared in a sterile solution of 0·9% saline (1 mg/ml) and given in incremental doses of 0·05 mg/kg every two minutes to a maximum of 0·25 mg/kg. Ninety of the 117 episodes were terminated. This included 88 of the 102 episodes of junctional tachycardia (79 of the 92 episodes of atrioventricular reentry tachycardia, seven of the eight episodes of atrioventricular nodal reentry tachycardia, and both of the episodes of long R–P′ tachycardia). Only one of four episodes of His bundle tachycardia and one of the eight episodes of ectopic atrial tachycardia were terminated. None of the three episodes of atrial flutter were terminated. Side effects were frequent but mild and included transient complete atrioventricular block (<6 s), sinus bradycardia (<40 s), ventricular extrasystoles, flushing, nausea, headache, and respiratory disturbance. Reinitiation (within 5 s) of supraventricular tachycardia occurred in 13 of the terminated episodes.

Although reinitiation limited its clinical efficacy in some patients, intravenous adenosine offered a safe and efficient method of rapid termination of most episodes of supraventricular tachycardia and in some cases facilitated diagnosis of the mechanism.

Adenosine is a short-acting purine nucleoside with the potential to slow conduction through the atrioventricular node and suppress the automaticity of atrial and Purkinje tissues. It has been used successfully for treatment and diagnosis of adults[1] and seems to compare favourably with more traditional agents.[2] We have followed up a preliminary report on its use in infants and children.[3]

Patients and methods

One hundred and seventeen episodes of supraventricular tachycardia in 50 children (29 male and 21 female; aged one day to 17 years (median two months) were treated with adenosine. Twenty eight were under one year of age. The results in four of the children were reported in an earlier preliminary communication.[3]

In most, the mechanism of tachycardia was diagnosed from the surface electrocardiogram. The criteria used included the relation of the P wave to the QRS complex, the P wave axis, and the presence or absence of QRS alternans during tachycardia.[4] In some children recordings from temporary oesophageal or epicardial (after surgery) electrodes were used to assist diagnosis. Seven children underwent a full electrophysiological study by standard methods.

Twenty eight children had atrioventricular reentry tachycardia (overt pre-excitation in 12, concealed in 16), eight had atrioventricular nodal reentry tachycardia, one incessant long R–P′ tachycardia, three His bundle tachycardia, three atrial flutter, and eight ectopic atrial tachycardia. One child had both His bundle tachycardia and atrial flutter on two different occasions; both were treated with adenosine. Twenty seven children had a structurally normal heart. Table 1 shows the anatomical details of the other 23.

In most children vagal manoeuvres and other forms of standard treatment had been tried unsuccessfully. One hundred and thirteen of the 117 episodes of supraventricular tachycardia occurred spontaneously. The other four episodes of tachycar-

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Table 1 *Data on children with structural abnormalities of the heart*

Anatomical diagnosis	*Operation*	*Arrhythmia*	*No of children*
TGA	Mustard	AVRT	2
		HBT	1*
		AFl	2*
	Arterial switch	AVNRT	1
		EAT	2
	Senning	AFl	1
		EAT	1
TGA plus pulmonary stenosis	Blalock shunt	EAT	1
Ebstein's anomaly	—	AVRT	2
Common arterial trunk	Correction	HBT	1
Tetralogy of Fallot	—	AVNRT	1
Aortic stenosis	—	Long R–P′	1
	Valvotomy	EAT	1
AV, VA discordance, pulmonary atresia	Blalock	AVRT	1
Idiopathic dilated right atrium	—	EAT	1
VSD, subaortic stenosis	Closure VSD, resection of muscle bar	AVRT	1
DILV	Fontan	EAT	1
Hypoplastic left heart	Norwood (1st stage)	AVNRT	1
Myocardial necrosis of unknown origin	—	HBT	1
Multiple tumours	—	AVRT	1

*One child had both atrial flutter and His bundle tachycardia.
AVRT, atrioventricular reentry tachycardia; AVNRT; atrioventricular nodal reentry tachycardia; HBT, His bundle tachycardia, EAT, ectopic atrial tachycardia; AFl, atrial flutter; TGA, transposition of the great arteries; VSD, ventricular septal defect; DILV, double inlet left ventricle.

dia were induced during electrophysiological study.

Adenosine was prepared as a sterile solution in 0·9% sodium chloride (1 mg/ml). The initial dose was 0·05 mg/kg given intravenously. This was increased in increments of 0·05 mg/kg to a maximum dose of 0·25 mg/kg or until termination was achieved. Each bolus was flushed immediately with physiological saline. The electrocardiogram was recorded throughout administration of the drug. Blood pressure was monitored immediately before and immediately after each bolus either by sphygmomanometer or by direct intra-arterial measurement.

Children receiving other antiarrhythmic drugs were included in the study, as were 20 children in overt cardiac failure, eleven of whom required inotropic agents to maintain a satisfactory blood pressure. Children were excluded from the study if they were asthmatic (or had a strong family history of asthma) or if they had a history of complete atrioventricular block.

One child received an infusion of adenosine in an attempt to control a postoperative His bundle tachycardia. This was tried when an intravenous bolus unexpectedly resulted in successful transient termination of the tachycardia. The infusion was given into the right internal jugular vein. A dose of 0·05 μg/kg/min was given initially and increased in stages to a maximum dose of 0·3 μg/kg/min. Heart rate and blood pressure were monitored continuously—blood pressure through an indwelling intra-arterial cannula in the femoral artery and a catheter in the pulmonary artery.

Results

Ninety (77%) of the 117 episodes of supraventricular tachycardia were terminated (table 1). Collectively 88 (86%) of the 102 episodes of junctional tachycardia (that is atrioventricular reentry tachycardia, atrioventricular nodal reentry tachycardia, and long R–P′ tachycardia) were terminated and 79 (86%) of the 92 episodes of atrioventricular reentry tachycardia. Analysis of the surface electrocardiogram recorded during termination confirmed that the mode of termination was a block in the atrioventricular nodal limb of the reentry circuit in most cases. In six episodes termination resulted from a block in the accessory pathway (fig 1) in four infants previously treated with class 1 drugs (flecainide and disopyramide) who still had appreciable blood concentrations of these agents and in two children who had received no other antiarrhythmic drug. Seven of the eight episodes of atrioventricular nodal reentry tachycardia were terminated by adenosine. Only one of these episodes occurred during an electrophysiological study and on this occasion termination was the result of slowing in the slow anterograde limb of the circuit. The long R–P′ tachycardia terminated in the retrograde limb of the reentrant circuit on two occasions. Only one each of the four episodes of His bundle tachycardia and of the eight episodes of ectopic atrial tachycardia were terminated by adenosine. No episodes of atrial flutter were terminated, but transient slowing of the ventricular rate resulted from an increased degree of atrioventricular nodal block (fig 2).

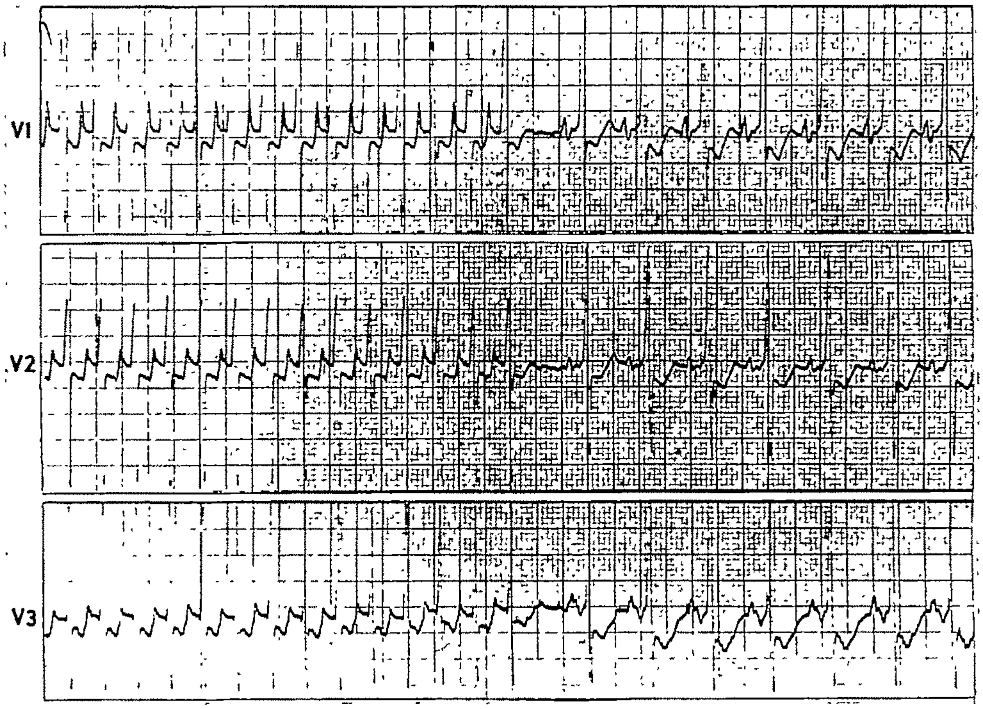

Fig 1 *Termination of orthodromic atrioventricular reentry tachycardia in the retrograde limb of the reentry circuit after infusion of intravenous adenosine in a neonate receiving oral flecainide. Paper speed 25 mm/s.*

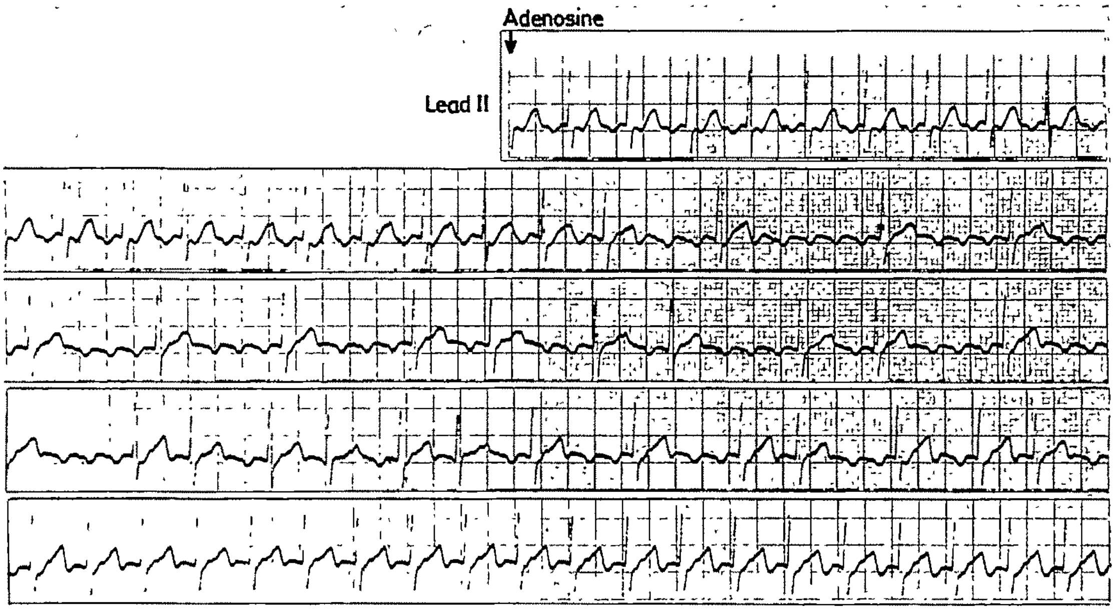

Fig 2 *A continuous electrocardiogram showing the effects of adenosine in an infant with atrial flutter. Transient slowing of atrioventricular nodal conduction reveals flutter waves on the surface electrocardiogram. Paper speed 25 mm/s.*

Adenosine produced a rapid conversion to sinus rhythm in those patients in whom it was effective; the time to termination ranged from 6 to 20 s (median 12 s). This was noticeably shorter if the agent was administered into a central vein rather than peripherally. The dose required ranged from 0·05 mg/kg to 0·25 mg/kg (median 0·15 mg/kg). Many of the 50 children (117 episodes) were given adenosine on more than one occasion. Eight children received adenosine on more than two occasions. In these we were able to make some assessment of the variation in the response within individual patients. In general, adenosine either worked every time or failed repeatedly, and in those in whom it was successful a very similar dose could be used on each occasion. The administration of other oral drugs, however, often changed the response to adenosine.

COMPLICATIONS

There were no important complications after an intravenous bolus of adenosine in our patients but relatively mild and unsustained side effects were common. A transient disturbance of respiration and flushing were common but not distressing. One child complained of nausea and headache. One infant, who was inadvertently given a maximum dose of adenosine as the first dose, experienced a sinus bradycardia of 40 beats per minute after termination, but the heart rate returned to normal within 40 s. In a further two patients transient complete atrioventricular block developed immediately after termination but this resolved within 6 s (fig 3). After a Mustard procedure in a child who before the onset of supraventricular tachycardia had long episodes of junctional rhythm, termination was followed by a junctional escape rhythm. Ventricular couplets and ventricular extrasystoles were seen in six children but were not responsible for termination of tachycardia in any. No patient had atrial fibrillation or chest pain and no intervention was required for these shortlasting complications. We did not detect a fall in blood pressure after an intravenous bolus in any patient; instead blood pressure tended to increase after reversion to sinus rhythm.

In patient 16 with His bundle tachycardia, transient termination was achieved with a bolus of adenosine (0·2 mg/kg). The arrhythmia had developed two hours after complete repair of common arterial trunk and gave rise to a low cardiac output requiring support with high doses of catecholamines. The child was receiving anaesthetic drugs to suppress activity and assist ventilation at this time. The infusion of adenosine resulted in a fall in heart rate from 224 to 207 beats per minute but was accompanied by a fall in both systolic (maximum fall 29 mm Hg) and diastolic (maximum fall 10 mm Hg) blood pressure. All variables returned to normal within 15 seconds of the end of the infusion. This was the only child in whom blood pressure fell.

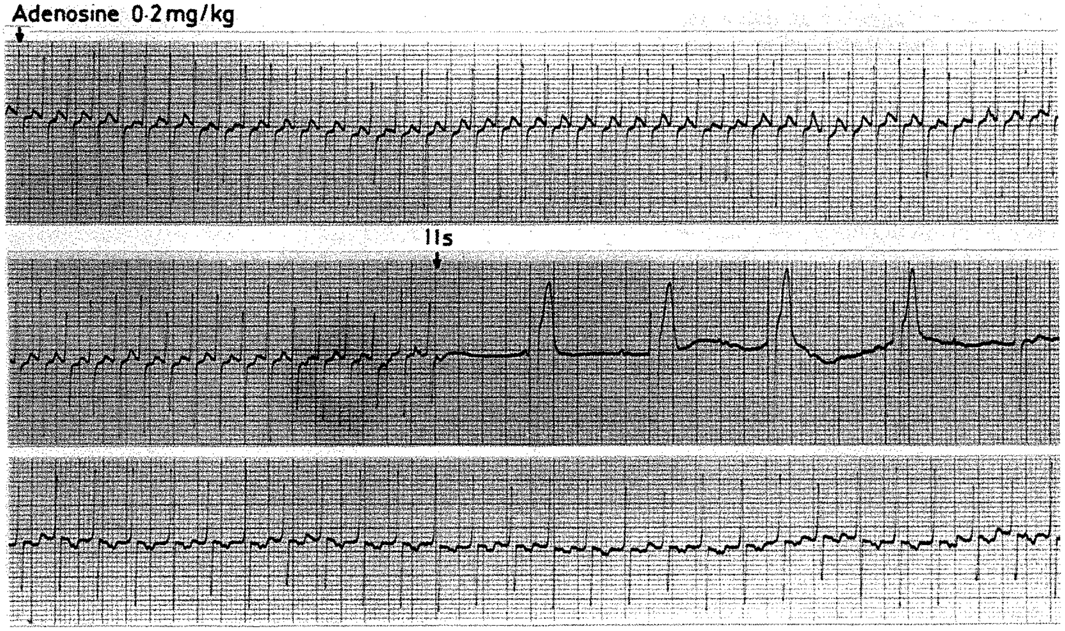

Fig 3 *Transient complete atrioventricular block after termination of atrioventricular nodal reentry tachycardia. Continuous rhythm strip lead V2. Paper speed 25 mm/s.*

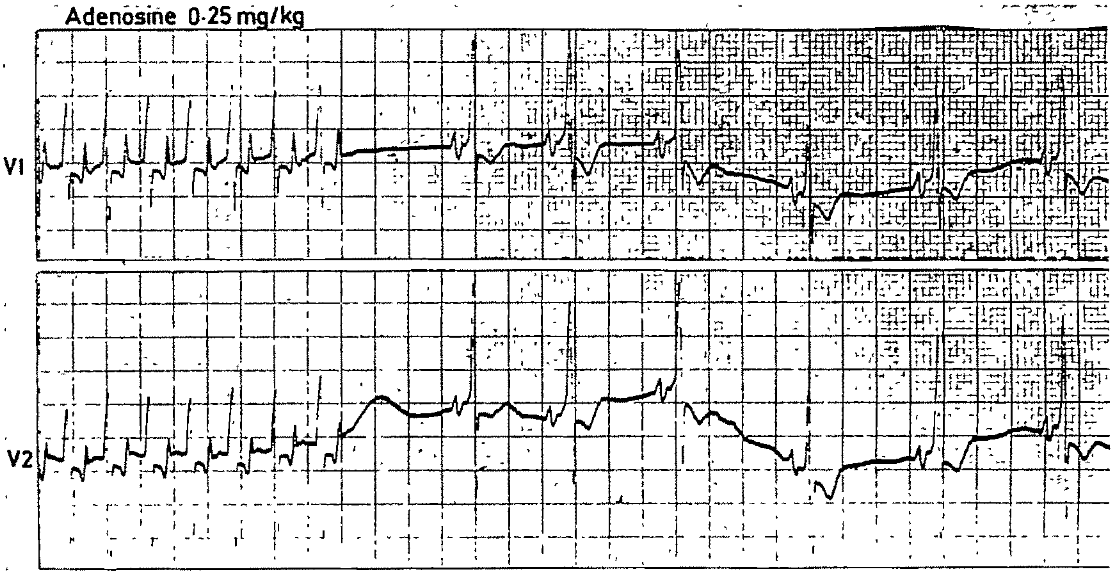

Fig 4 *Termination of orthodromic atrioventricular reentry tachycardia in the atrioventricular nodal limb of the reentry circuit after adenosine. Transient pre-excitation can be seen after termination in this neonate with "latent" Wolff-Parkinson-White syndrome. Paper speed 25 mm/s.*

ROLE IN DIAGNOSIS

In eight children with "concealed" pre-excitation and atrioventricular reentry tachycardia, termination of the arrhythmia was followed by a transient delay in atrioventricular nodal conduction. This allowed preferential anterograde conduction via an accessory pathway, which showed itself on the surface electrocardiogram for the first time (fig 4). Thus adenosine allowed confirmation of a diagnosis of "latent" pre-excitation and atrioventricular reentry tachycardia. Similarly in nine children, after termination of the tachycardia, ventriculoatrial conduction via the accessory pathway resulted in "retrograde" P waves (atrial echoes) on the surface electrocardiogram. The relation of these with the QRS complex again aided the diagnosis of the mechanism of supraventricular tachycardia. In two of the three episodes of atrial flutter the mechanism of supraventricular tachycardia was not appreciated until the administration of adenosine, but because adenosine caused a transient delay in the conduction of the atrioventricular node, flutter waves could be seen clearly on the surface electrocardiogram—thus establishing the diagnosis.

COADMINISTRATION OF OTHER DRUGS

Adenosine was administered to 20 children who had received digoxin in the previous 24 hours, to five children who still had therapeutic concentrations of amiodarone, to five children undergoing treatment with oral flecainide, and to two receiving oral disopyramide. No adverse effects were seen in any of them. One patient was already receiving an aminophylline infusion at the time of administration of adenosine. We had expected that this child might have required a higher dose of adenosine for termination because aminophylline is known to compete at cell surface receptors[5]; however, conversion to sinus rhythm was achieved with a dose of 0·05 mg/kg.

Table 2 *Results of adenosine infusion in 50 infants and children with supraventricular tachycardia*

Arrhythmia	*No of children*	*No of episodes*	*No of episodes successfully terminated*	*Sustained termination*
AVRT	28	92	79 (86%)	71 (77%)
AVNRT	8	8	7 (87%)	6 (75%)
EAT	8	8	1 (12·5%)	0
HBT	3	4	1	0
AFl	3	3	0	0
Long R–P′	1	2	2	0
Total	50	117	90 (77%)	77 (66%)

See footnote to table 1 for abbreviations.

REINITIATION

Rapid reinitiation of supraventricular tachycardia was seen in 13 of the 90 episodes terminated by adenosine. This occurred in four tachycardias known to be incessant (long R–P′, His bundle tachycardia, and ectopic atrial tachycardia) but also in nine episodes of paroxysmal tachycardia. Sustained termination was therefore achieved in 66% of all cases (75% of all episodes of junctional tachycardia—that is 77% of atrioventricular reentry tachycardia, 75% of atrioventricular nodal reentry tachycardia, and none of the episodes of His bundle tachycardia or ectopic atrial tachycardia).

Discussion

Adenosine is a purine nucleoside with a half life in humans of <15 s. The full role of endogenous adenosine remains to be elucidated. It may be an important regulator in many systems.[6] In vitro, adenosine depresses the conduction of the atrioventricular node and the automaticity of the atrial and Purkinje fibres, hyperpolarises the membrane, and shortens the action potential of atrial myocytes.[7] These actions may be used to terminate attacks of supraventricular tachycardia, and the related compound adenosine triphosphate has been used in such a way for many years.[8 9] It has recently become clear that many of the actions of adenosine triphosphate result from its rapid breakdown to adenosine. There is some evidence to suggest that some actions of the two compounds are mediated by different purinergic receptors,[10] and indications that side effects may be worse with adenosine triphosphate[11] have prevented its widespread acceptance.

The success of both these agents in the termination of junctional tachycardia lies in their ability to interrupt the critical timing necessary for continuation. In our series adenosine proved highly effective in these arrhythmias, with an immediate termination rate of 86%. In atrioventricular reentry tachycardia delay within the circuit occurred predictably in the atrioventricular nodal limb in most cases.

Termination of orthodromic atrioventricular reentry tachycardia in the retrograde limb of the circuit was an intriguing and unexpected finding because adenosine has little direct action on myocardial tissue in vitro. Possible explanations are that the accessory pathways in such young patients have different physiological properties and are sensitive to adenosine or that the accessory pathway is sensitised to the effects of adenosine by prior treatment with class 1 drugs. Overholt and colleagues also saw this phenomenon in a few of the children they treated with adenosine[12] but as they suggested, without intracardiac recordings, it is impossible to exclude the possibility of an accessory pathway with decremental (atrioventricular nodal) properties on the basis of the electrocardiogram alone, even though the surface electrocardiogram during tachycardia was not typical of such a tachycardia. Similarly, we suggest that it is not possible to exclude the induction of atrial extrasystoles, by adenosine, which are blocked, and therefore not manifest on the surface recording, but which would effectively terminate a reentry tachycardia.

Adenosine was not as successful with other types of arrhythmia, confirming the findings of Overholt and colleagues.[12] Perelman and Krikler recently reported a case in which ectopic atrial arrhythmia was terminated by adenosine triphosphate and they suggested this agent may act directly on the atrial myocytes.[13] In one patient in whom there was an automatic focus of atrial tachycardia in our series adenosine was successful. Although adenosine was seldom effective in terminating these arrhythmias, the disclosure of continuing tachycardia in the presence of variable degrees of transient atrioventricular block was useful in diagnosis. Three of the four patients with His bundle tachycardia were resistant to treatment although a fourth was terminated transiently, prompting a trial of continuous adenosine infusion. Importantly, adenosine did not cause the acceleration that may be seen when verapamil is used in such a tachycardia.

We report the results of an open trial of the use of adenosine. This was not a comparative study. None the less, many of the patients had not responded to more conventional drugs given before adenosine. For many years digoxin has been regarded as the best drug to treat supraventricular tachycardia in childhood and particularly in infancy. Unlike most other agents it is not negatively inotropic and thus may be administered safely when arrhythmias are complicated by severe impairment of cardiac output. However, its use is not without complications and more recently its efficacy has been questioned.[14] Because there may be a considerable delay before termination is achieved it is possible that termination is spontaneous rather than the result of a direct drug action; and at an arbitrary time limit of two hours its efficacy is estimated to be less than that of other agents (71% digoxin, 87% adenosine triphosphate, 93% verapamil).[15] Digoxin can enhance the development of arrhythmias after direct current countershock, and when it is given to treat ventricular tachycardia mistakenly diagnosed as supraventricular tachycardia it can cause ventricular fibrillation. Verapamil has been shown to be highly effective in the short term treatment of supraventricular tachycardia[16 17] but is contraindicated in the presence of myocardial disease, recent treatment with β blockers, and sick sinus syndrome. In recent reports the efficacy of both adenosine and adenosine triphosphate compared favourably with that of verapamil.[18] Undoubtedly some of the problems reported with verapamil in children have been secondary to its inappropriate use[19] but some have suggested profound collapse of infants under one year of age after intravenous verapamil.[20 21] It has been speculated that this may be the result of increased sensitivity to verapamil in young patients.[22] In addition, like digoxin, if verapamil is given mistakenly during ventricular tachycardia it may result in ventricular fibrillation and may cause acceleration of a His bundle tachycardia.[23] It seems from our work and that of Griffith *et al*[24] that adenosine may be safely given in both these circumstances.

Side effects with adenosine were common during treatment but they were acceptable because they were transient. We attempted to exclude children with sick sinus syndrome because we anticipated the effects of adenosine on sinus node automaticity. Two children who had undergone a Mustard procedure and later developed sinus node dysfunction, however, were admitted to the study. No adverse effects were seen in these patients. This is in contrast with the findings of Overholt and his colleagues who included in their trial one child with diffuse disease of the conduction system and found a prolonged sinus bradycardia without an adequate escape rhythm after adenosine.[12] They suggested that children with underlying dysfunction of the sinus or atrioventricular node should be treated with caution because their patient needed temporary ventricular pacing.

The children with impaired cardiac output, including those receiving catecholamine infusions, showed no sustained fall in blood pressure after an intravenous bolus of adenosine, and yet an infusion of adenosine in one patient resulted in a fall in both systolic and diastolic blood pressure. Because of these seemingly conflicting results it is worth discussing the effects of adenosine on the cardiovascular system, as far as they are known. Adenosine is a potent vasodilator, acting through specific vascular receptors and this effect is seen in anaesthetised patients and used to produce controlled hypotension during neurosurgical procedures.[25] In conscious individuals, however, this vasodilator action is not usually manifest. In a recent study by Biaggioni *et al* a bolus of adenosine in conscious adult volunteers resulted in a biphasic blood pressure response with an initial increase in both systolic and diastolic pressure at 27 seconds followed by a fall approximately 10 seconds later.[26] This fall in pressure (maximum 9 mm Hg systolic and 12 mm Hg diastolic) was accompanied by an increase in heart rate. An infusion of adenosine in the same volunteers resulted in a dose dependent increase in heart rate with little change in mean blood pressure. The same group then studied adults with autonomic failure and found quite different results in that a bolus dose of adenosine resulted in a fall in blood pressure and bradycardia. They concluded that the masking of the direct vasodilator effects of the agent in conscious patients results from an autonomic reflex possibly mediated by chemoreceptors in the carotid body. After a similar dose of adenosine, we did not detect a fall in blood pressure, whether or not the children were receiving anaesthetic drugs. However, this may reflect the inaccuracies of our method, because in most children blood pressure was measured with a sphygmomanometer rather than by direct intra-arterial cannulation, and there was usually a short delay before the measurement could be taken. A transient increase in heart rate after termination was usual. Nevertheless, the lack of a sustained fall in blood pressure after a bolus of adenosine indicated that it may be of particular use in infants and children with poor cardiac output when most other antiarrhythmic agents would be contraindicated. The one child who received a continuous infusion of adenosine while under general anaesthesia did show a decrease in blood pressure and heart rate corresponding to the observations of Biaggioni and colleagues[26] and this hypotension limited its therapeutic value.

In junctional tachycardias (atrioventricular reentry, atrioventricular nodal reentry, and long R–P′) we achieved an immediate termination of 86% of episodes and this was sustained in 75%. Reinitiation of supraventricular tachycardia may limit the clinical efficacy of this agent. A possible mechanism for this effect is the sinus acceleration that follows a bolus dose. This is a common mechanism of initiation of supraventricular tachycardia in small infants.[27] A further explanation is that the heart rate increases as a result of central sympathetic activation as a reaction to unpleasant side effects, which in adults are acceptable because they are transient.[1] Interestingly, Overholt *et al* did not comment on this phenomenon and reported a 100% success rate in such arrhythmias.[12] This may be because many of their children were either sedated or receiving a general anaesthetic at the time of adenosine administration. Although efficacy was limited in some children by immediate reinitiation of tachycardia, the short half life had major advantages in other respects; side effects were inevitably shortlived and repeated administration in those children with rapidly recurring supraventricular tachycardia was safe. We used adenosine in conjunction with oral amiodarone, disopyramide, flecainide, and digoxin with no additional adverse effects and believe it may prove useful in the management of recurrent tachycardia in patients already being treated with other antiarrhythmic agents when adequate therapeutic concentrations had not yet been achieved.

We showed that adenosine was a safe agent in the treatment of paediatric supraventricular tachycardia and rapidly terminated most episodes. It was highly effective in junctional tachycardias and was safe to use in other less common arrhythmias. It offers many advantages in terms of its diagnostic and treatment successes and adverse effects over presently available drugs for the treatment of childhood supraventricular tachycardia, but therapeutic efficacy may be limited in some cases by rapid reinitiation of supraventricular tachycardia.

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Variability of the Doppler gradient in pulmonary valve stenosis before and after balloon dilatation

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SUMMARY The variability of the valve gradient measured by Doppler in pulmonary stenosis was compared with the variability of the gradient measured at catheterisation in 42 infants and children undergoing catheterisation with a view to balloon dilatation of the pulmonary valve. The maximum value measured by Doppler when the patient was unsedated was significantly higher than that measured when the patient was sedated for catheterisation, and the maximum gradient was significantly higher shortly after than several days later. In a patient with pronounced infundibular obstruction after dilatation the Doppler signal clearly showed that the obstruction was dynamic, with a superimposed lower fixed signal that correctly predicted the final low gradient.

The Doppler gradient in an alert and unsedated patient may be a better measure of the true physiological value. The highest Doppler value so obtained is a more appropriate indicator of the need for balloon dilatation than a single catheter measurement. The result of dilatation is best assessed by Doppler measurement at least a day after the procedure.

Doppler echocardiography accurately estimates the severity of pulmonary valve stenosis,[1-3] and the agreement with the results of catheterisation is best when both measurements are performed simultaneously.[3 4] This indicates that gradients vary under different physiological conditions. It has been generally accepted, but not confirmed, that the gradient in an alert and possibly apprehensive patient can be higher than that measured when the patient is sedated at catheterisation.

Decisions on the need for intervention have previously been based on the transvalvar gradient measured at catheterisation in sedated patients. But the values of the Doppler gradient may be different in an alert patient, and this might influence decisions on the need for or results of dilatation.

We report our findings with Doppler ultrasound in 42 patients with pulmonary valve stenosis undergoing catheterisation to establish whether they needed balloon dilatation. We wanted to see whether the measured gradient was different in sedated patients and whether it changed between the period immediately after dilatation (under sedation) and later follow up.

Patients and methods

A series of 42 patients aged six days to 15 years (mean 4 years 10 months) underwent cardiac catheterisation to assess their suitability for balloon dilatation of the pulmonary valve. In six patients dilatation was not undertaken because the physician considered that the gradient was not clinically significant. Dilatation was attempted in the remaining 36: one infant with critical pulmonary stenosis became hypotensive when the guide catheter traversed the pulmonary orifice, and it subsequently proved impossible to pass the balloon catheter into the pulmonary artery; the gradient seemed little changed by the procedure in five patients and reduced in the remaining 30.

Catheterisation was performed under sedation with either a mixture of pethidine, promethazine, and chlorpromazine as a single intramuscular injection or oral phenobarbitone followed by a single intramuscular dose of papaveretum and hyoscine. Right ventricular and pulmonary arterial pressures were measured through fluid filled catheters attached to strain gauge transducers either simultaneously through two catheters or by withdrawal across the valve.

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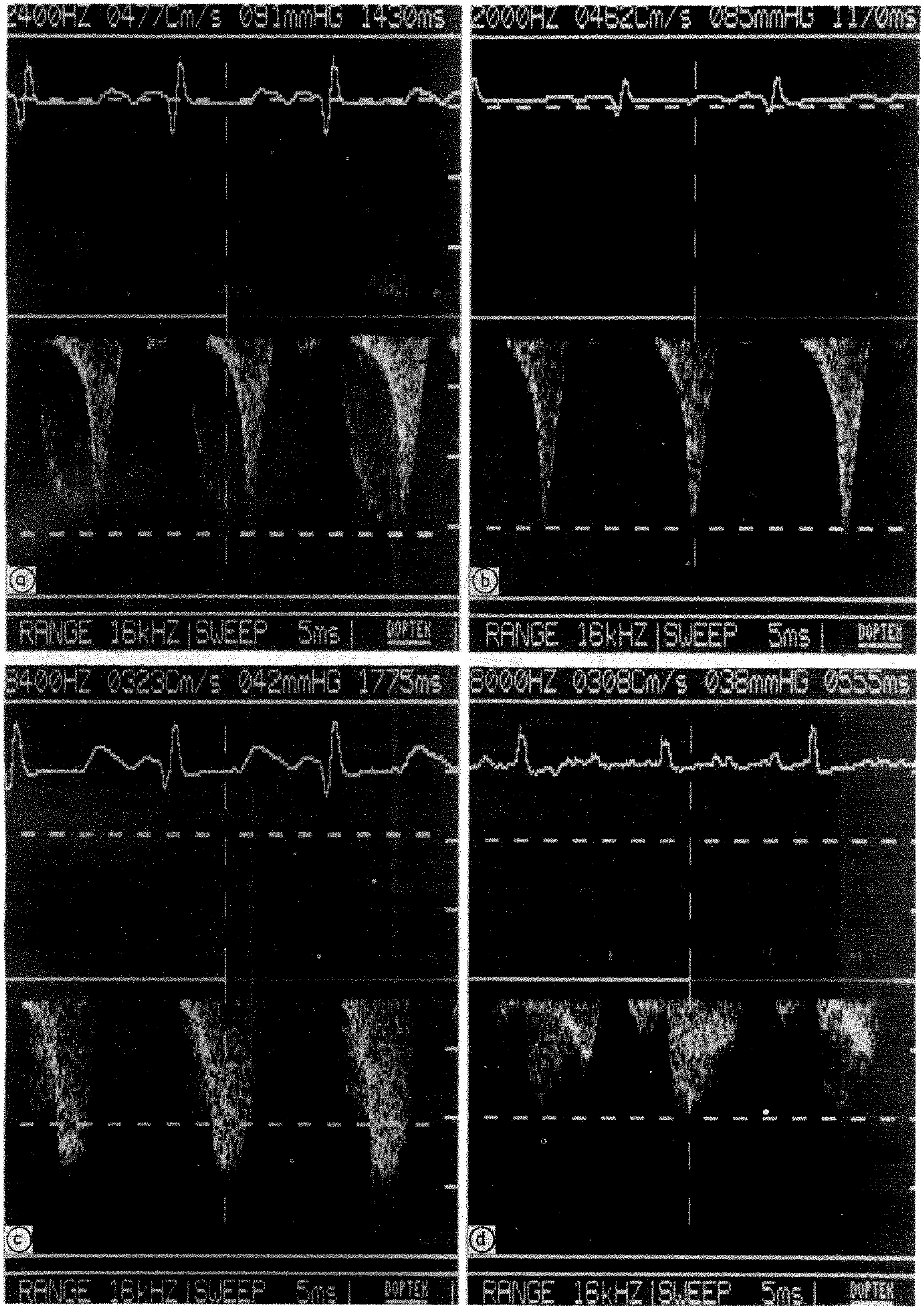
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RANGE 16kHZ | SWEEP 5ms | DOPTEK
RANGE 16kHZ | SWEEP 5ms | DOPTEK

Fig 1 *Spectral recordings from a three month old patient with pulmonary valve stenosis and significant subvalvar dynamic muscular obstruction. Before dilatation (a) the dynamic concave signal (equivalent to a gradient of 85 mm Hg) was superimposed on the signal indicating fixed obstruction (91 mm Hg), but (b) was shown more clearly by adjustment of transducer angulation. Immediately after (c) the dynamic concave signal (85 mm Hg) remained but the fixed one was reduced to 42 mm Hg, but (d) 6 weeks later the gradient was 38 mm Hg with a low dynamic signal, equivalent to 12 mm Hg.*

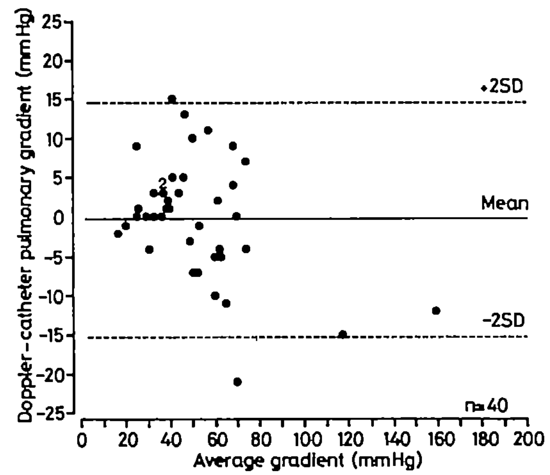

Fig 2 *Comparison of the difference between gradients (Doppler minus peak to peak) and the average gradient obtained at the time of catheterisation before balloon dilatation in 40 patients.*

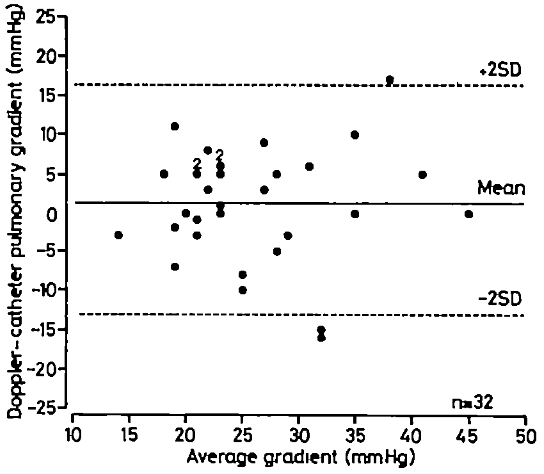

Fig 3 *Comparison of the difference between gradients (Doppler minus peak to peak) and the average gradient obtained at the time of catheterisation after balloon dilatation in 32 patients.*

Doppler studies were performed with either a non-imaging Alfred Velocimeter (Vingmed) interfaced to a Doptek spectrum analyser or a Vingmed CFM 700 system with imaging and colour flow mapping. The entire left parasternal edge and the subxiphoid and suprasternal positions were explored and the position and angulation of the probe adjusted to obtain the maximum reproducible velocity signal showing the high velocity signals with a clear and complete envelope. Simultaneous electrocardiographic monitoring was used to exclude maximal frequency shifts caused by extrasystoles. The maximum frequency shift was measured from the Doppler signal and the maximum velocity (V) was derived and the pressure drop (P) estimated from the modified Bernoulli formula, $P = 4V^2$.

For further confirmation of the accuracy of our technique we compared Doppler values with simultaneous peak to peak pressure gradients before dilatation was attempted and just before the catheters were removed after dilatation. The difference between the values was calculated, the mean difference (and standard deviation) for the studies obtained, and the individual differences were plotted against the average values by the method of Bland and Altman.[5]

Then the highest Doppler estimate of the pressure drop obtained without sedation was compared with the value when the patient was sedated at catheterisation before dilatation, and the Doppler measurement 15 to 45 minutes after the procedure was compared with the value ≥ 1 days later.

Full Doppler and catheter studies were not available for review from every patient: Doppler gradients measured with and without sedation were available in 38; simultaneous Doppler and catheter gradients before dilatation in 40 (29 dual catheter and 11 withdrawal) and immediately after dilatation in 32 (25 dual catheter and seven withdrawal); and Doppler gradients immediately and ≥ 1 days after the procedure in 30.

Results

DOPPLER FLOW PATTERNS

When patients were under sedation before dilatation all the Doppler records showed the typical parabolic appearance of fixed obstruction, with a lower velocity concave (or scimitar) signal of dynamic obstruction clearly superimposed in six. The dynamic obstruction was relatively unimportant being < 20 mm Hg in all but two. In one it was 100 mm Hg for both the fixed and dynamic gradient and in the other patient the dynamic obstruction was 85 mm Hg and the fixed obstruction was 91 mm Hg (fig 1 a and b). In this last patient the fixed element was 42 mm Hg and the dynamic element was 85 mm Hg immediately after dilatation (fig 1c); single catheter measurements showed a total pressure drop of 130 mm Hg between the pulmonary artery and ventricle—40 mm Hg from the pulmonary artery to a subvalve chamber and 90 mm Hg from there to the ventricle. The spectral signal was interpreted as indicating that the valve narrowing was sufficiently reduced but there was still appreciable dynamic infundibular obstruction, and we predicted that the dynamic obstruction would resolve leaving a final gradient of about

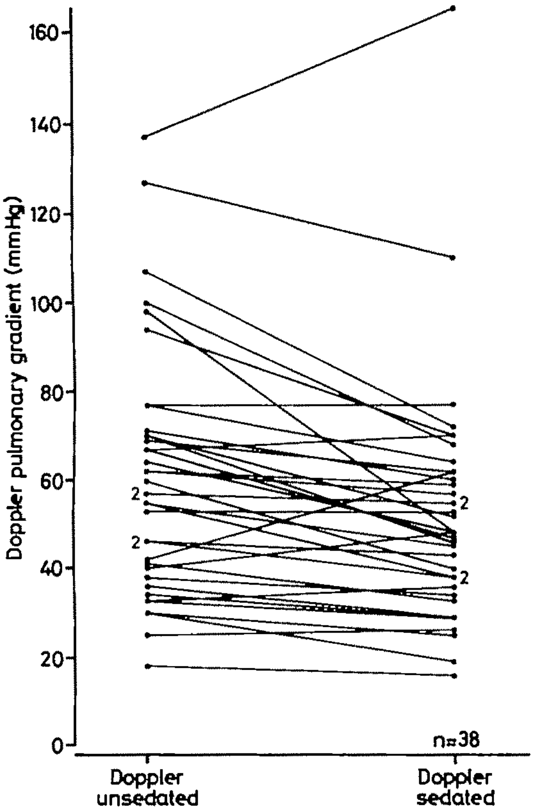

Fig 4 *Differences between maximum Doppler gradient obtained in unsedated patients before balloon dilatation and that measured at catheterisation in 38 sedated patients.*

40 mm Hg; four months later the Doppler gradient was 38 mm Hg with only a minor dynamic component (12 mm Hg) (fig 1d).

COMPARISON OF DOPPLER VALUES WITH PEAK TO PEAK MAXIMUM GRADIENT

Comparison of these by the method of Bland and Altman[5] gave the mean difference (2 SD) between methods before dilatation of − 0·1 (15·0) mm Hg (fig 2) and of 1·2 (14·6) mm Hg after dilatation (fig 3).

COMPARISON OF DOPPLER VALUES IN THE SEDATED AND UNSEDATED STATE

The maximum values for the Doppler gradients with the patient unsedated were compared with those measured under sedation in 38 patients (fig 4) by a paired *t* test on the differences between values measured with and without sedation. The mean difference between sedated and unsedated values (2 SD) (8·2 (3·7) mm Hg) was statistically significant (p <0·01). In general the values in unsedated patients were higher. In 22 patients the values without sedation were within 10 mm Hg of the values measured under sedation, in 14 cases the value in the unsedated patient was > 10 mm Hg higher, and in only two patients was it > 10 mm Hg less.

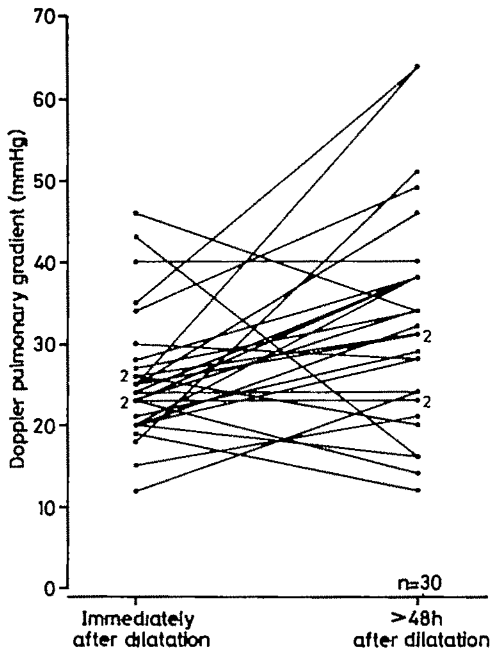

Fig 5 *Doppler gradient measured in 30 sedated patients immediately after balloon dilatation and the value at least two days later.*

COMPARISON OF DOPPLER VALUES IMMEDIATELY AND > 1 DAY AFTER DILATATION

The patient with considerable residual infundibular obstruction (see below) was excluded. In the remaining 30 patients (fig 5) a two tailed paired *t* test on the differences between Doppler values shortly after dilatation and > 24 hours after was significant (p < 0·01) (mean difference (2 SD), 6·8 (5·0) mm Hg). These results show that the values obtained immediately after dilatation were significantly lower than those 24 hours after the procedure. The changes in Doppler values were > 10 mm Hg in 11 cases. The greatest difference was in a patient who had a pulmonary valve gradient of 35 mm Hg by Doppler (measured as 35 mm Hg peak to peak) shortly after dilatation, but which rose to 64 mm Hg 48 hours after the procedure.

Discussion

Doppler ultrasound accurately measures the transvalvar gradient in pulmonary valve stenosis,[1-4] and the decision on whether to proceed to dilatation is now based on a Doppler gradient obtained when the patient is active, usually at an outpatient visit, rather than on catheter measurements of pressure under sedation. It is essential to have clear knowledge of possible changes in gradient that can result from this.

This study confirmed the accuracy of Doppler in comparison with simultaneous catheter readings but showed that the gradient usually fell with sedation: in most cases this fall was small (< 10 mm Hg) and of little clinical significance but in some it can be so large that the gradient is no longer considered to be of clinical significance. Is the gradient measured under sedation an appropriate one on which to base the decision on the need for dilatation? We believe that it is more logical to use the highest value, even if this is obtained in an unsedated patient, because this will more accurately reflect the true physiological condition.

Robertson *et al* found no significant alteration in gradients measured immediately after dilatation and several days later but gave only the mean of the gradients in a group of 18 patients.[6] Our study indicates that changes do occur, as shown by the *t* test, although in only two of the 30 was this change of clinical significance.

We found a statistically significant difference between the Doppler gradients measured in the active and the sedated states before and after dilatation, and it is important to consider these changes when patients are selected for dilatation or the results of this procedure are assessed. We consider the highest gradient, whether measured in a patient who is awake or sedated, is the most appropriate for selecting patients for dilatation and that a repeat Doppler study several days thereafter is essential in assessing the final result.

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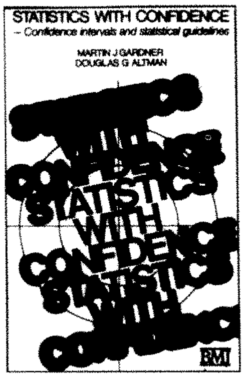
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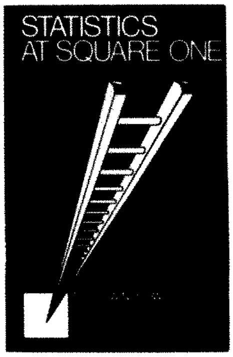

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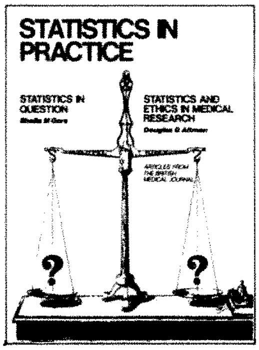
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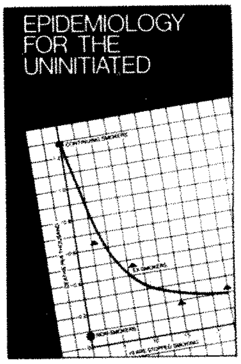

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Case reports

Use of streptokinase to aid in drainage of postoperative pericardial effusion

JUDITH H CROSS, JOSEPH V DE GIOVANNI, ERIC D SILOVE

From the Department of Cardiology, Children's Hospital, Birmingham

SUMMARY A case of cardiac tamponade secondary to a late, loculated pericardial effusion after open pulmonary valvotomy is described. Percutaneous drainage of the effusion was aided by the infusion of intrapericardial streptokinase.

Pericardial effusion causing cardiac tamponade occurs in quite a few patients after open heart surgery. Rapid diagnosis and treatment are essential to prevent the associated high morbidity. Loculation of fluid may hinder drainage and relief. We report a case in which percutaneous infusion of a fibrinolytic agent aided drainage of such an effusion and may have prevented reaccumulation of fluid.

Case report

A boy with Noonan's syndrome presented with severe valvar pulmonary stenosis and hypertrophic obstructive cardiomyopathy when he was 15 months old. Balloon dilatation of the pulmonary valve at the age of 16 months resulted in only a slight reduction in gradient. He, therefore, underwent open pulmonary valvotomy with right ventricular homograft patch four months later.

Although he had coexistent interstitial pneumonitis (requiring low dose oral prednisolone) he initially did well and was extubated on the eighth postoperative day. A mild degree of heart failure responded promptly to diuretic treatment. Steroid treatment was maintained throughout. On day 16, however, tachypnoea developed with faint heart sounds and hepatomegaly. There was no pyrexia or leucocytosis at any time. An echocardiogram showed a large pericardial effusion of depth 1·5 cm posterior to the left ventricle; this was best seen on the left parasternal short axis view. Straw coloured fluid (75 ml) was drained percutaneously. Repeat echocardiography showed a reduction in effusion depth to 0·96 cm. Initially he improved but on day 21 he deteriorated quite suddenly with clinical signs of cardiac tamponade.

The recurrence of a large pericardial effusion (depth 2·8 cm) posterior to the left ventricle with cardiac compression was confirmed on the echocardiogram. On this occasion thick fibrinous strands could be seen traversing the pericardial space (figs 1

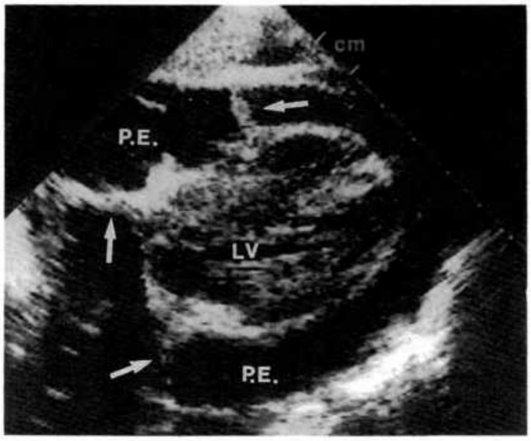

Fig 1 *Short axis view across body of left ventricle showing large pericardial effusion with fibrin strands (arrowed). Concentric hypertrophy of the left ventricle is present. PE, pericardial effusion; LV, left ventricle.*

Requests for reprints to Dr Judith H Cross, Birmingham Children's Hospital, Ladywood Middleway, Birmingham B16 8ET.

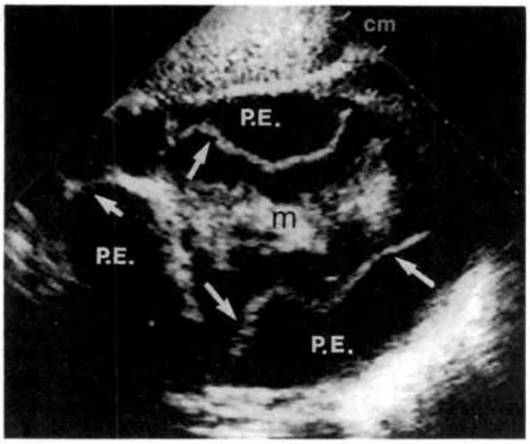

Fig 2 *Short axis cut close to cardiac apex showing loculation of large pericardial effusion by fibrin (arrowed). M, apical myocardium; PE, pericardial effusion.*

and 2). A cannula was inserted into the pericardium percutaneously from below the xiphisternum, and 130 ml of bloodstained fluid was withdrawn. The cannula was left in place and allowed to drain. A further 40 ml was withdrawn four hours later, and then 2000 units of streptokinase was infused into the pericardial sac. The drain was clamped for three hours and then allowed to drain freely. The next day a further 2000 units of streptokinase was infused. The drain was removed on day 23. Repeat echocardiograms on days 23, 25, and 38 showed no reaccumulation of pericardial fluid.

Discussion

Pericardial effusion has been reported in as many as 56% patients after open heart surgery,[1] with cardiac tamponade occurring in up to 4%. Such effusions may occur in the early postoperative period, usually associated with acute bleeding, or more than seven days after operation. The incidence of cardiac tamponade in late effusions is only 0·25—2·6%.[2]

Late effusions have many causes. Most are likely to be the result of residual thrombus after pericardiotomy.[2] Thrombus has a higher osmolality than plasma and draws fluid from the intravascular compartment into the pericardial space. Some effusions may be secondary to accumulation of pericardial fluid caused by post-pericardiotomy syndrome, which was reported in 1·6—50% of patients[3 4]; the wide variation in this frequency probably results from problems in absolute definition and overlap. The diagnosis of cardiac tamponade may be confused with congestive cardiac failure. Cross sectional echocardiography is usually diagnostic, but pericardial clot compression without fluid may cause tamponade and can be difficult to identify by echocardiography. Rapid diagnosis and effective management of cardiac tamponade are essential because outcome can be fatal.

Our patient did not have a pericardial effusion in the immediate postoperative period but signs of cardiac tamponade, requiring drainage, developed on day 16. On further accumulation of fluid, fibrinous organisation of the effusion was noted on cross sectional echocardiography. The child showed no signs of postpericardiotomy syndrome such as fever, apparent pain, or leucocytosis. Steroids may have suppressed these signs, but they should also have suppressed any inflammatory process causing accumulation of pericardial fluid. The fibrinous strands suggested that organised thrombus was the likeliest cause. Complete drainage of fluid was prevented by loculation and reaccumulation of the effusion was likely.

Streptokinase has been used intrapleurally for over 30 years to aid drainage of loculated empyema,[5] without inducing any systemic fibrinolytic effect.[6] There is one report of haemorrhage after intrapleural administration but the existence of a bronchopleural fistula may have predisposed the patient to systemic absorption of streptokinase.[7] After forming a complex with plasminogen, streptokinase combines with fibrin and activates subsequent thrombolysis. In our patient, intrapericardial infusion of streptokinase aided effective percutaneous drainage of an organised pericardial effusion, with relief of cardiac tamponade, and it may also have prevented a recurrence. We suggest that intrapericardial streptokinase has a role in the management of late postoperative pericardial effusions, particularly when fluid is loculated by fibrin strands. None the less, the technique should not be used where there is evidence of inflammation, which may enhance absorption of the enzyme and increase the risk of haemorrhage.

We thank Mr L D Abrams for his advice on the management with extravascular streptokinase.

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Development of multiform ventricular tachycardia during atrioventricular nodal reentrant tachycardia

DAVID H BENNETT,* CORMAC COYLE†

*From the *Regional Cardiac Centre, Wythenshawe Hospital, Manchester and †Leighton Hospital, Crewe, Cheshire*

SUMMARY A woman of 18 presented with a supraventricular tachycardia, subsequently shown to be caused by atrioventricular nodal reentry, which abruptly deteriorated to a multiform ventricular tachycardia. She had not received any antiarrhythmic drugs nor did she have any of the disorders that are usually associated with this atypical ventricular tachycardia.

To our knowledge, the association between multiform ventricular tachycardia and atrioventricular reentrant tachycardia has not been described before.

Case report

The patient is an 18 year old woman with an eight year history of weekly episodes of rapid palpitation, lasting between half and six hours. On one occasion these had caused syncope. Her father had died suddenly and was known to have had hypertrophic cardiomyopathy. There was no other relevant family history.

For the first time, an electrocardiogram was recorded during palpitation when she recently presented to a casualty department. It showed a regular tachycardia with narrow ventricular complexes at a rate of 188 beats/min. During the recording the rhythm abruptly changed to a multiform ventricular tachycardia (fig 1), which lasted for 30 seconds, after which sinus rhythm returned (fig 2). The patient did not experience dizziness or syncope. Neither oral nor parenteral antiarrhythmic drugs had been administered. She was taking an oral contraceptive but no other drugs.

Electrocardiograms recorded during sinus rhythm were normal. The QTc interval (0·42 s) was towards the upper limit of normal. Echocardiography was normal and there was no suggestion of hypertrophic cardiomyopathy: during diastole the interventricular septum and posterior left ventricular wall were both 1·0 cm thick.

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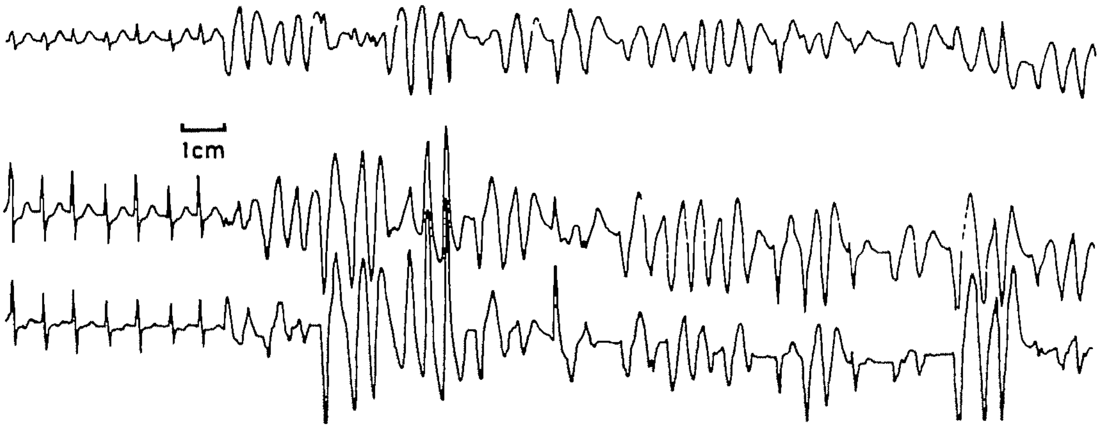

Fig 1 *Electrocardiogram with leads I, II, and III recorded simultaneously at 25 mm/s. Supraventricular tachycardia abruptly changed to multiform ventricular tachycardia.*

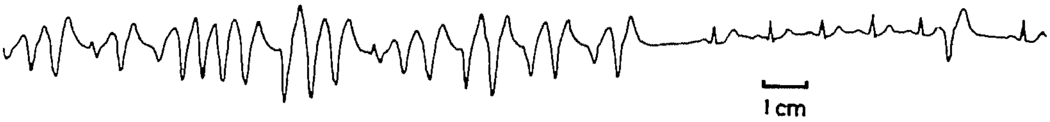

Fig 2 *Electrocardiogram showing restoration of sinus rhythm 30 seconds after initiation of multiform ventricular tachycardia.*

An intracardiac electrophysiological test was carried out. No evidence of an accessory atrioventricular pathway was found: during ventricular pacing, the ventriculoatrial conduction time increased progressively with increasing prematurity of the ventricular stimulation. Atrioventricular reentrant tachycardia was repeatedly initiated and terminated by precisely timed premature atrial extrastimuli. During tachycardia, the earliest evidence of atrial activation was seen in the His bundle electrogram and coincided with ventricular depolarisation, suggesting that tachycardia was caused by atrioventricular nodal reentry. Multiform ventricular tachycardia did not arise at the termination of the supraventricular tachycardia and was not provoked by rapid atrial pacing or by single and double premature stimuli introduced at the right ventricular apex. The supraventricular tachycardia was repeatedly terminated by a scanning anti-tachycardia pacemaker that introduced a series of seven premature atrial stimuli: ventricular tachycardia was not precipitated.

She did not tolerate oral sotalol, and oral verapamil in a dose of 40 mg three times a day and flecainide 100 mg twice a day were ineffective. The patient refused further antiarrhythmic drugs. A scanning anti-tachycardia atrial pacemaker was implanted (PASAR 4171, Telectronics). Since implantation, episodes of palpitation have been brief and no ventricular arrhythmias have been seen during ambulatory electrocardiography.

Discussion

Multiform ventricular tachycardia may be caused by abnormalities in ventricular repolarisation, by bradycardias, and by antiarrhythmic drugs[1] (when it is termed "torsade de pointes"), and also by myocardial infarction.[2] It has not previously been described in association with atrioventricular reentrant tachycardia. It is noteworthy that ventricular tachycardia was precipitated on only one occasion by the supraventricular tachycardia.

Supraventricular extrasystoles have been reported to initiate uniform ventricular tachycardia[3] and, after acute myocardial infarction, ventricular fibrillation.[4] Multiform ventricular tachycardia has been initiated in patients with anterograde ventricular pre-excitation[5] and ventricular fibrillation has been reported in two patients with hypertrophic cardiomyopathy and associated accessory atrioventricular pathways.[6] But there was no evidence of myocardial infarction, pre-excitation, or hypertrophic cardiomyopathy in our patient in whom the mechanism of initiation of multiform ventricular tachycardia during atrioventricular tachycardia is unclear.

We thank Dr J Hall for his help and for referral of this case.

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Straddling tricuspid valve without a ventricular septal defect

YUKIHISA ISOMATSU, HIROMI KUROSAWA, YASUHARU IMAI

From the Department of Paediatric Cardiovascular Surgery, Heart Institute of Japan, Tokyo Women's Medical College, Tokyo, Japan

SUMMARY A four year old girl with pulmonary atresia had a straddling tricuspid valve without an interventricular communication. The overriding tricuspid valve had two orifices, which connected with the right and the left ventricles. Valve tissue separated both orifices and was firmly connected to the crest of the ventricular septum, thus sealing off the expected interventricular communication. Surgical correction was performed and the outcome was satisfactory.

A straddling tricuspid valve is an infrequent congenital malformation, which by definition is almost always associated with an underlying ventricular septal defect. Recently, however, we have operated on a patient with pulmonary atresia and a straddling tricuspid valve with two separate orifices and no interventricular communication.

Case report

When the patient was born in May 1982, she weighed 2·6 kg. She showed cyanosis immediately after birth. Non-invasive diagnosis showed pulmonary atresia with intact ventricular septum and a ductus arteriosus. Her condition improved when prostaglandin E_1 was given. When she was two months old a left Blalock-Taussig shunt and pulmonary valvotomy were performed and when she was four months old an aortopulmonary shunt was performed.

At the age of four years she was admitted for definitive surgical repair. The echocardiogram showed a hypoplastic right ventricle and a tricuspid valve that straddled into the left ventricle (fig 1). Preoperative catheterisation showed raised right ventricular pressure (86/7 mm Hg) caused by residual pulmonary stenosis; the systemic pressure was 98/49 mm Hg. The right ventricular end diastolic volume was 44% of the expected normal range.

Surgical correction was undertaken. A Glenn

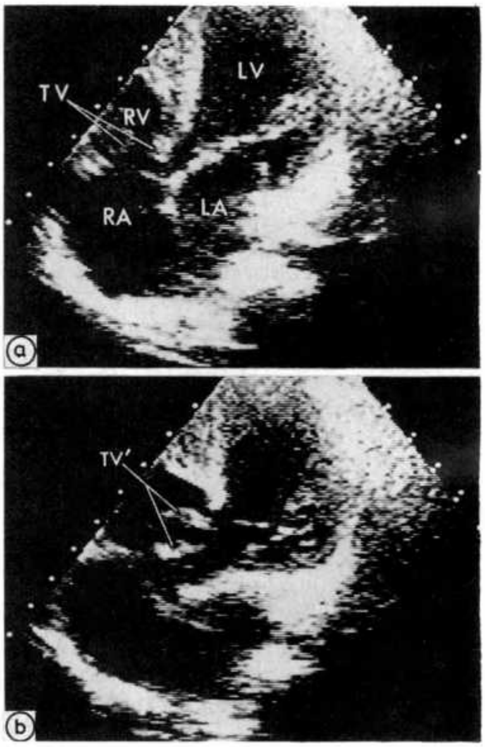

Fig 1 *Preoperative echocardiograms. (a) Four chamber view showing a tricuspid valve (TV) connecting the right atrium (RA) to both hypoplastic right ventricle (RV) and left ventricle (LV). (b) Straddling tricuspid valve (TV) opening into left ventricle. LA, left atrium.*

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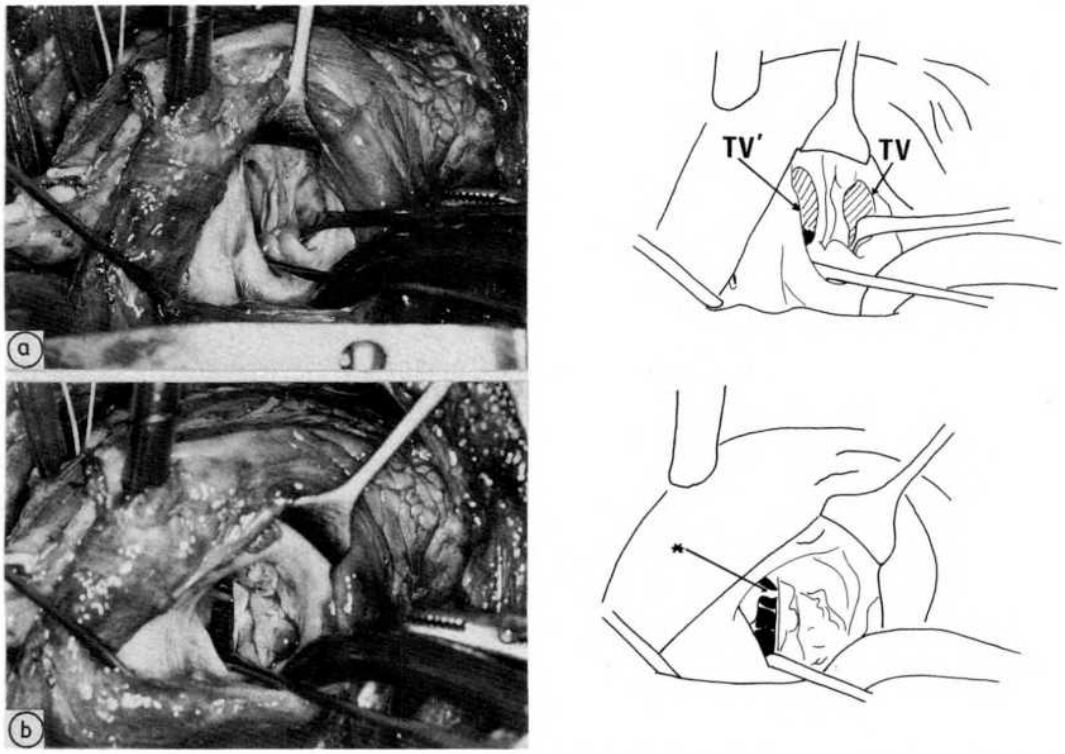

Fig 2 *Intraoperative pictures. (a) There are two orifices of the tricuspid valve (TV, TV'). A connecting tongue of fibrous tissue is seen between both orifices. (b) The tension apparatus of the posterior leaflet of the tricuspid valve is inserted into the posterior papillary muscle of the mitral valve (*).*

procedure in which the right pulmonary artery was divided and anastomosed to the superior vena caval vein was performed through a median sternotomy. Pump perfusion was started and the left Blalock-Taussig shunt and aortopulmonary shunt were taken down. The tricuspid valve was closely examined through a right atriotomy (fig 2). The diameter of the valve orifice was 27 mm. It overrode the ventricular septum. Approximately two thirds opened into the left ventricle, so that the atrioventricular connection was designated as a double inlet into a left ventricle. The second chamber had right ventricular morphology and was positioned to the right. The inlet part of the ventricular septum did not extend to the crux, but deviated to the right. The anterior leaflet of the straddling portion was devoid of chordae. However, the tension apparatus of the posterior leaflet was inserted into the posterior papillary muscle of the mitral valve. Despite the straddling of the tricuspid valve, there was no interventricular communication because the anterior and posterior parts were connected by valve tissue, itself firmly adherent to the crest of the inlet septum. The arrangement resembled that seen in hearts with an atrioventricular septal defect and two orifices (so called partial variety or ostium primum defect). The ventriculoarterial connection was concordant. In addition, there were associated malformations—for example pulmonary atresia, hypoplastic right ventricle, and atrial septal defect.

The orifice connecting the right atrium to the left ventricle was closed with preserved bovine pericardium. We took care not to injure the atrioventricular node which because of the straddling tricuspid valve was likely to be anomalously sited. Because the remaining right sided tricuspid orifice seemed to be too small to cope with all the inferior venous return we did not ligate the junction between the superior caval vein and the right atrium. The right ventricular outflow tract to the left pulmonary artery was reconstructed with a monocusp patch.

Postoperative catheterisation showed a mean right atrial pressure of 14 mm Hg and a mean pulmonary arterial pressure of 13 mm Hg. She was discharged at 31 days after operation and her condition remains stable.

Discussion

A straddling atrioventricular valve can occur as an associated anomaly in various types of congenital heart disease and may cause serious complications, particularly when during surgical correction of the basic deformity. Double outlet right ventricle, complete transposition, congenitally corrected transposition, and double inlet ventricle are well known examples.[1-3] Almost always there is a large interventricular communication underneath the straddling valve and this usually makes it difficult to close the defect and preserve valve function.

A straddling tricuspid valve without an accompanying ventricular septal defect is extremely rare.[4] Our patient had an overriding and straddling tricuspid valve with pulmonary atresia, but otherwise normal atrioventricular and ventriculoarterial connections. The tension apparatus of the posterior leaflet of the straddling tricuspid valve was inserted into the posterior papillary muscle of the mitral valve. The potential interventricular communication, however, was closed by a connecting tongue of valve tissue that adhered firmly to the crest of the ventricular septum, as it does in partial atrioventricular septal defects. Thus two ostia were formed. The larger one emptied into the left ventricle and the smaller one led into the right ventricle. The atrioventricular connection was therefore designated as double inlet into a left ventricle.

Indeed, double inlet left ventricle is often complicated by atrioventricular valve malformations, including straddling of the right sided or tricuspid valve. We are unaware, however, of any other reports of patients with such a cardiac malformation, further complicated by pulmonary atresia, in which the interventricular communication underneath the straddling valve was anatomically sealed.

The arrangement may have resulted from incomplete transfer of the inlet component of the developing ventricle. The developing anterior and posterior leaflets of the tricuspid valve may have become fused by the development of valve tissue along the crest of a well developed inlet septum. Thus the connecting tongue may have eventually fused with the ventricular crest, resulting in closure of the interventricular communication before birth.

The present observation is of interest to clinicians and surgeons and to those interested in the morphogenesis of congenital heart malformations.

We thank Professor A E Becker for his advice.

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Subacute rupture of a pseudoaneurysm formed by late rupture of a true left ventricular aneurysm

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SUMMARY A man aged 34 in whom rupture of a true aneurysm at least four weeks after acute myocardial infarction led to the development of a pseudoaneurysm is described. Because the pseudoaneurysm ruptured subacutely and the haemodynamic, clinical, and echocardiographic signs were not consistent, diagnosis of the cardiac rupture was delayed. Operative repair was successful, but the patient died.

Left ventricular aneurysm is a common complication after myocardial infarction. Because false aneurysms (pseudoaneurysms) often rupture it is important to distinguish them from true aneurysms.[1] Late rupture of a true aneurysm is unusual and subsequent formation of a pseudoaneurysm on its surface must be rare. We describe the diagnostic difficulties of this unusual complication of a myocardial infarction.

Case report

A 34 year old man was transferred from another hospital because of suspected cardiac rupture. Three months before he had suffered an acute anterior myocardial infarction from which he made an uneventful recovery. At that time haemoglobin was 171 g/l. Soon after infarction he completed a 7 min exercise test without symptoms but 2 mm ST depression was noted in lead III. He was discharged home and was treated with atenolol (50 mg daily).

Four weeks later he was readmitted because of left sided chest pain, which was aggravated by deep inspiration and eased by sitting and leaning forward. His pulse rate was 65 beats per minute and blood pressure 100/60 mm Hg. A pericardial friction rub was heard. The haemoglobin concentration was 143 g/l, the white blood cell count was 9·100/mm^3, and the erythroctyte sedimentation rate 44 mm/h. Precordial Q waves consistent with the evolution of the anterior myocardial infarction were present on the electrocardiogram, which was essentially unchanged from the electrocardiogram on discharge. There was no rise in the activity of cardiac enzymes. Cardiac antibodies were negative and a ventilation-perfusion scan was normal. At a repeat test he exercised for 8 min with no ST segment depression. A gated isotope cardiac scan was consistent with an anterior aneurysm and poor left ventricular function (fig 1). A possible diagnosis of Dressler's syndrome was made and the patient was treated with aspirin and discharged home. The pain persisted in the left lower anterior chest. It varied in intensity and was aggravated by coughing and deep inspiration.

Two months after infarction the patient was readmitted because of severe retrosternal pain, which worsened with inspiration, and associated dyspnoea. The haemoglobin concentration was 134 g/l, the white blood count was 12·600/mm^3, and the erythrocyte sedimentation rate was 45 mm/h. The electrocardiogram and chest radiograph were unchanged. The activity of cardiac enzymes was normal. During a test he exercised for 8 min with no ST segment changes. He was discharged home on

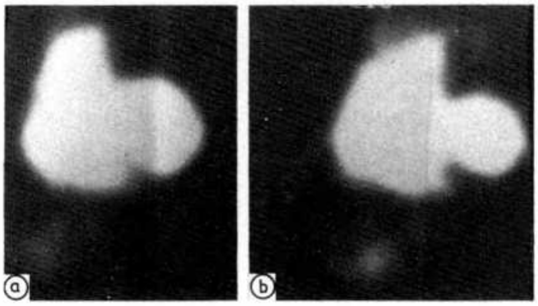

Fig 1 *Gated pool scans four weeks after myocardial infarction during (a) systole and (b) diastole. A large left ventricular aneurysm is present.*

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ibuprofen. He continued to experience pain at home.

Two days before he was transferred to our hospital sudden severe pain developed in the epigastrium and he collapsed with incontinence of faeces. He was admitted to the same hospital again. He was sweaty but there was no vomiting or melaena. The patient was pale, distressed, but conscious. His pulse rate was 116 per minute and blood pressure 100/60 mm Hg. The epigastrium was tender on palpation with guarding and rebound tenderness. An echocardiogram showed a moderate pericardial effusion and an apical ventricular aneurysm. Metabolic acidosis (lactate acid 8·7 mmol/l) was found. The patient was transferred to this hospital the next day with a provisional diagnosis of a leaking ventricular aneurysm.

The patient smoked 20 cigarettes a day and weighed 95 kg. There was no history of hypertension or diabetes. Examination showed a conscious, pale, unwell young man with poor peripheral perfusion. His temperature was 36·7°C, pulse 100 per min, respiration rate 20 per min, and blood pressure 100/60 mm Hg with a 15 mm Hg paradox. Jugular venous pressure was raised 15 cm but Kussmaul's sign could not be detected. The heart was enlarged, with a diffuse apical impulse, and a third heart sound was present. A pericardial friction rub was audible. A few rales were audible in both lung bases. The epigastrium was tender and the bowel sounds quiet. The haemoglobin was 106 g/l and the total serum creatine kinase was 149 IU/l. The electrocardiogram showed signs of an old anterior myocardial infarction, without alteration in voltage. Chest *x* ray showed cardiomegaly. An echocardiogram showed pericardial effusion with no signs of diastolic collapse of the right ventricle and an apical left ventricular aneurysm.

Cardiac catheterisation showed the following pressures: right atrium 26/18 mm Hg (mean 24), right ventricle 45/20 mm Hg; pulmonary artery 45/20 mm Hg (mean 30), pulmonary artery wedge pressure 30/16 mm Hg (mean 24), left ventricle 95/22 mm Hg, and aorta 100/70 mm Hg.

There was a deep x descent and a blunted y descent in the right atrial pressure waveform. A decrease in intra-aortic pressure of 10 to 15 mm Hg during inspiration was recorded. A coronary arteriogram showed that the left anterior descending artery was totally occluded proximally. Left ventriculography showed a huge, true, anterior left ventricular aneurysm (fig 2). There was a suggestion of an opening in the apex of the true aneurysm (fig 2) but no evidence of contrast entering the pericardial space, and no definite conclusion about the cause of the tamponade could be reached. Pericardiocentesis was attempted but was unsuccessful.

The patient was transferred to the operating theatre and sternotomy was performed. The pericardial cavity was full of old clot surrounding the heart. A false aneurysm was present at the apex of the heart. This was firmly contained by the pericardium and it was ruptured at one site. A large thrombus was present in the lumen of the true aneurysm. After removal of the thrombus the aneurysm was excised and patched under cardiopulmonary bypass. The patient died soon after the operation with signs of left ventricular failure.

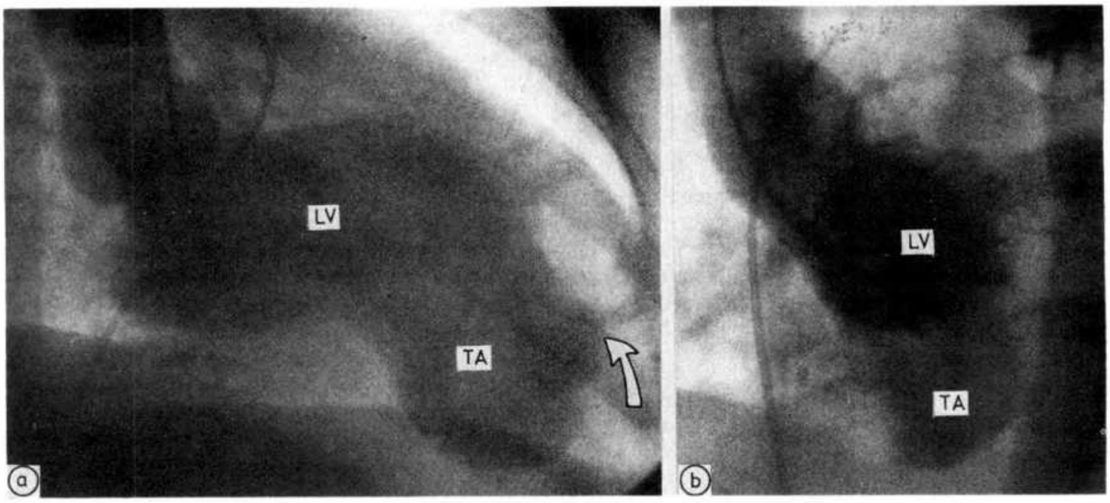

Fig 2 *Left ventriculograms in (a) the right anterior oblique and (b) the left anterior oblique projections. LV, functioning left ventricle; TA, true aneurysm. The arrow indicates the site of the pseudoaneurysm.*

At necropsy the prosthetic patch was in position at the apex of the heart. The myocardium showed irregular fibrosis in the anterior wall of the left ventricle and the anterior half of the interventricular septum; the endocardium covering this area showed fibrous thickening. The histological appearance was consistent with this being an area of left ventricular infarction undergoing some resolution by fibrosis. The left anterior descending artery was occluded by old organised thrombus that completely filled the proximal 3 cm of the vessel. Recent, non-adherent thrombus was present in the left main artery extending to the vessel wall, and on cut section pale and dark areas were seen. The cause of death was believed to be left ventricular failure caused by peroperative embolisation of the left main stem and circumflex coronary arteries.

Discussion

Attention has been drawn to the difficulty in distinguishing between true and false ventricular aneurysms.[1] Rupture of a left ventricular aneurysm is uncommon and occurs in the early stages of development. Late rupture, when the aneurysm has become stabilised by the formation of dense fibrous tissue in its wall, almost never occurs.[2] We found only one report of a case of rupture of a true ventricular aneurysm at least a month after acute myocardial infarction.[3]

In contrast with true aneurysm, both large and small pseudoaneurysms may rupture during the early stages of development and also after the established fibrous stage is reached.[2] The rupture may lead either to sudden fatal pericardial haemorrhage or to recurrent haemorrhagic effusion.[4]

The sequence of events in our patient is not clear. We believe that a true aneurysm developed after the acute myocardial infarction and was confirmed by gated pool scan four weeks later. At that stage the true aneurysm probably ruptured. Rupture was complicated by pericarditis and subsequent formation of the pseudoaneurysm. It is possible that there was a minor rupture of the pseudoaneurysm two months after the myocardial infarction and that this led to recurrent pericardial haemorrhage. But it is more likely that there was a major rupture of the pseudoaneurysm two months after its development (three months after the myocardial infarction) when the patient was admitted after collapse.

Our patient had classic haemodynamic findings of tamponade; but the classic clinical signs of tamponade, apart from raised venous pressure, were absent or were not pronounced. Echocardiography defined the true aneurysm but not the false aneurysm, and left ventriculography was suggestive of a false aneurysm. Good images were difficult to obtain in this obese patient. Despite the patient's continuing pain, the referring physicians were initially misled by the apparent well-being of the patient. London and London reported that repeated and prolonged chest pain was a feature in 55% of patients with cardiac rupture,[5] possibly because of slow leakage of blood into the pericardial sac before clinically evident cardiac tamponade.

Although in most cases of cardiac rupture death is instantaneous, our patient survived at least 24 hours, long enough to reach the operating theatre. This outcome accords with the suggestion that cardiac rupture may be subacute and that when it is diagnosed during life it can be corrected surgically.[6]

We thank Dr D S Reid for his help in preparing this paper and for allowing us to report this case.

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Balloon dilatation of a stenosed modified (polytetrafluoroethylene) Blalock-Taussig shunt

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SUMMARY A 17 month old girl with tricuspid atresia, ventricular septal defect, subvalvar and valvar pulmonary stenosis, and increasing cyanosis had angiographic evidence of proximal stenosis of a right modified (5 mm diameter) Blalock-Taussig shunt. She underwent palliative balloon angioplasty with a 6 mm Schneider balloon catheter. Successful dilatation was achieved without complication. Four months later there was subjective clinical improvement with a rise in systemic arterial saturation. Repeat angiography showed patency of the shunt without restenosis or formation of an aneurysm.

Balloon angioplasty has been used as a palliative treatment for the relief of baffle obstruction after Mustard's operation,[1] in patients with symptomatic tetralogy of Fallot,[2] and after stenosis of classic Blalock-Taussig shunts.[3] We report successful balloon dilatation of a stenosed modified Blalock-Taussig shunt (polytetrafluoroethylene graft) in a 17 month old girl with tricuspid atresia, ventricular septal defect, and subvalvar and valvar pulmonary stenosis.

Case report

A baby girl weighing 3·6 kg presented with central cyanosis when she was six days old. Physical examination showed an ejection systolic murmur maximal along the lower sternal border. The electrocardiogram showed sinus rhythm, a superior mean QRS frontal axis, and left ventricular dominance. Cross sectional echocardiography showed tricuspid atresia with concordant ventriculoarterial connections, a non-restrictive ventricular septal defect, a hypoplastic right ventricle, and subvalvar and valvar pulmonary stenosis. She was initially managed conservatively but after three months she became increasingly cyanosed and underwent a modified right Blalock-Taussig shunt with a 5 mm diameter polytetrafluoroethylene graft.

When she was 17 months old increasing cyanosis and a haemoglobin concentration of 17·6 g/l prompted cardiac catheterisation, which showed aortic oxygen saturation of 73%. The main pulmonary artery pressure was 10/7 mm Hg (mean 8) with a simultaneous aortic pressure of 100/50 mm Hg (mean 60). Angiography showed moderate stenosis of the modified Blalock-Taussig shunt at the site of the proximal anastomosis (fig 1). There was acquired pulmonary atresia and the pulmonary arteries were of normal size with no evidence of localised stenosis or kinking. Balloon dilatation was performed. She was systemically heparinised with 50 IU/kg. A straight 0·020 inch exchange guide wire was passed from the

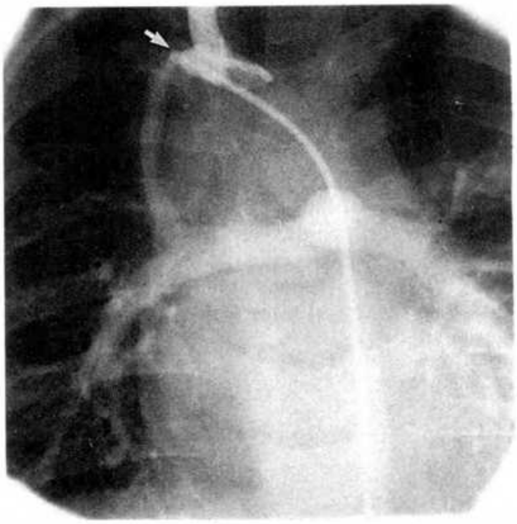

Fig 1 *Shunt angiogram in anteroposterior projection taken before balloon dilatation showing a right sided modified Blalock-Taussig shunt with a stenosis at the site of the proximal anastomosis to the right subclavian artery (arrow).*

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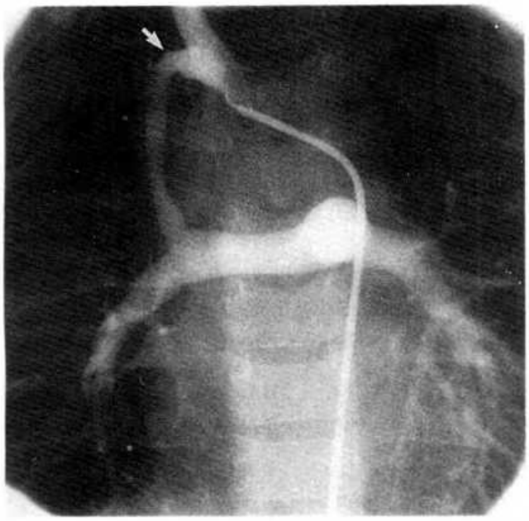

Fig 2 *Repeat shunt angiogram in anteroposterior projection taken four months after balloon dilatation showing effective relief of the previously stenotic site (arrow).*

femoral artery, into the descending aorta, through the shunt, and placed in the distal right lower lobe branch pulmonary artery. A Schneider balloon catheter (6 mm diameter, 15 mm balloon length) on a 5 French shaft was positioned across the site of the proximal stenosis and inflated twice. There were no complications either during or after inflation. Repeat angiography showed satisfactory relief of the proximal stenotic site. Pulse oximetry showed a transcutaneous oxygen saturation of 80% after the procedure. There were no early complications after this procedure and treatment with aspirin (10 mg/kg/24h) and dipyridamole (6 mg/kg/24h) was started.

Four months later, when she was 21 months old, she was less cyanosed. At repeat cardiac catheterisation the aortic oxygen saturation was 76%. Repeat angiography showed that the proximal anastomotic site was patent with no evidence of restenosis or formation of an aneurysm (fig 2).

Discussion

When at the age of 17 months our patient became more cyanosed and had angiographic evidence of a stenosed shunt, the therapeutic options included either a second systemic to pulmonary arterial shunt or a Fontan-type procedure. The younger a patient is when a Fontan-type operation is performed the higher the risk[4]; hospital mortality is 25% for operations carried out between 12 and 24 months.[5] Although the hospital mortality for a second shunt operation is likely to be low, complications such as distortion and kinking of the pulmonary artery[6] or pulmonary hypertension[7] may increase the operative risks of a subsequent Fontan-type procedure. Because balloon angioplasty was successful for palliation of patients with stenosed classic Blalock-Taussig shunts[3] we decided to use this technique in our patient to delay a Fontan-type procedure.

Balloon angioplasty achieved adequate palliation for four months without complications. There was an improvement in cyanosis, haemoglobin concentrations did not increase, and angiography did not show early restenosis or aneurysm formation. She remains suitable for a Fontan-type procedure.

There were no technical problems or complications associated with this procedure. The choice of balloon size was related to the size of the prosthetic shunt rather than specific angiographic measurements. For dilatation of a classic Blalock-Taussig shunt Fischer *et al* measured the diameter of the shunt immediately proximal to the stenosis and they found that a balloon with a diameter of equal size was ineffective; they used a balloon with a diameter that was 2 mm larger and a balloon to shunt ratio of 150%.[3] We recommend caution in using such a ratio for dilating prosthetic materials. Aneurysm formation and vessel and graft rupture are potential complications.

We believe that balloon angioplasty of stenosed modified Blalock-Taussig shunts is feasible and safe and may produce palliation in selected patients. Until further studies have been performed we advise caution in using balloon diameters that are larger than the shunt diameter.

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British cardiology

The roots of modern British cardiology

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The nineteenth century abounds with the names of individual British physicians expert in cardiac disease who wrote of its pathology, diagnosis, and management. As a group, however, they were not cardiologists as we would understand the term today; nor could they have been, when the new techniques available at the start of that century—percussion and auscultation—were just being added to the conventional methods—taking the history, inspection, and palpation. British interest in auscultation was immediate. Sir James Clark, who later attended John Keats the poet, acquired a stethoscope in Paris in 1818[1] and introduced Sir John Forbes to its use. Forbes translated (and modified) Laennec's book.[2] While he was still a student, William Stokes of Dublin wrote the first British book on the use of the stethoscope.[3] By 1819, stethoscopes were on sale in London,[1] being mainly used in diseases of the chest. And yet, as the century ended, cardiology was taking on the forms of a subspecialty of general medicine, not yet crystallised but in retrospect already evident. These physicians would not have labelled themselves as heart specialists, and often combined their interest in the heart with an interest in respiratory medicine and indeed even wider activities. Most of the consultant members on the staff of the original National Hospital for the Diseases of the Heart held appointments elsewhere that covered many other aspects of medicine.[4]

What then might have determined how cardiology developed? This can only be assessed in retrospect by identifying landmarks now known to have been important in leading to new methods of diagnosis and treatment. Similar events occurred in parallel in other European countries as well as the United States.

It is important to put matters into the perspective of the times. The events just mentioned occurred less than two centuries after Harvey's discovery of the circulation and less than half a century after two seminal advances—the introduction of digitalis by Withering[5] and the appreciation of the nature of angina pectoris through the observations of Heberden,[6] Jenner,[7] and Parry.[8] They coincided with the appearance of some of the classic texts on heart disease by leading British (and Irish) physicians of the first part of the nineteenth century, which reflected the clinical advances to that time: Burns, though primarily an anatomist, proposed the ischaemic theory of angina pectoris[9]; and Adams,[10] Hope,[11] Latham,[12] and Stokes[13] were the key authors of the textbooks of the day. These took account of the clinical developments to that time, but gradually, based on the new physiology that developed in France under Claude Bernard and Germany under Carl Ludwig, techniques were introduced that were to alter the study of heart disease and bring us to the cardiology—and cardiologist—of today. Participants in this process included the famous and the unrecognised, those actively and consciously engaged, and those whose contribution can only be acknowledged long afterwards. And even then, this can only be a selective account of some of the physicians and events concerned in the establishment of modern British cardiology. Lawrence has surveyed this period in some detail, with interesting philosophical insights. He focuses on changing attitudes at the basic as well as the clinical level,[14] and looks critically at developments from the perspective of the non-cardiologist.

Pulse recordings

Just when examination of the cardiovascular system was being improved by the greater use of devices to enhance the senses of touch and hearing, to assess structure, it became clear that there was also the need for the physician to assess the function of the circulation more appropriately. Not even Harvey had applied his concepts to the care of man, so it was timely that during the first half of the nineteenth century several physiologists tried to fill this gap and developed techniques for recording the pulse directly from the arteries and veins of living animals. Among

Based on the George Burch Memorial Lecture given to the Association of University Cardiologists, Carmel, California, on 19 January 1989.

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the foremost of these physiologists was Carl Ludwig of Leipzig, who taught the teachers—many of whom became pioneers of modern physiology. Closer to the clinical level was Etienne-Jules Marey of Paris, who made clinical recordings of the pulse from the surface of the intact body of a patient as early as 1857; his doctoral thesis of 1859 was cited by others even before he published his definitive study in 1863.[15] By 1870, Lorain was able to produce a substantial text on disorders of the pulse, comprising 372 pages and containing 488 figures. Most of the figures were pulse tracings made on drums of smoked paper.[16] He reviewed eleven major studies that had appeared in the preceding decade, several of them British (some individual parts of serial publications may have been cited separately yet others were missed). According to Foster, of Birmingham, the Marey sphygmograph was first demonstrated in Britain by Dr Hughes Bennett in Bath in 1864[17]: claims for priority led to acrimonious correspondence. John Burdon-Sanderson (soon to become professor of physiology at University College, London, and later Oxford) and Anstie wrote a series of major articles on pulse recordings, starting in 1866.[18] But a key figure in medical practice, Sir Lauder Brunton—then a medical student—had also started to use pulse tracings, and was soon to make other important contributions to cardiological practice.

When Thomas Lauder Brunton (1844–1916)[19] qualified from Edinburgh in 1866 he was preparing an MD thesis on digitalis that was published in 1868 and reprinted in his collected works.[20] In the preface to this collection he recalled that when he started his studies on digitalis there were only one or two of Marey's sphygmographs available in the United Kingdom. Burdon-Sanderson had not yet made one, but Brunton was able to borrow one from Arthur Gamgee (now remembered, if at all, for his layered bandage) who supervised his studies. Although these studies were performed barely 80 years after Withering's publication, digitalis had already fallen into neglect as a remedy for heart disease.[21] While Brunton continued to study the pulse—his subsequent work was cited by Mackenzie—at virtually the same time, and on the basis of what he gleaned from Gamgee, he discovered the value of the vasodilator amyl nitrite in angina pectoris.[22] This was soon to be supplanted by glyceryl trinitrate, which was introduced by Murrell of the Westminster Hospital,[23] but Brunton and his contributions should not be forgotten. He should also be remembered as one of the pioneer physiologists. On an extensive continental postgraduate tour in 1867–8 he included a visit to Ludwig in Leipzig, and in 1876 when Burdon-Sanderson invited the leading physiologists of the day to a meeting at his home to establish the Physiological Society, Brunton was one of those present.[24] Lawrence[14] stresses the importance of some of Brunton's other contributions, including his suggestion that mitral stenosis would prove amenable to surgical treatment; he clearly played an important role in the development of cardiology. The close links between physiology and clinical practice at that time are further attested by Burdon-Sanderson's career. He was successively Jodrell professor of physiology at University College, London, and Waynflete professor of physiology at Oxford before becoming regius professor of medicine there. He was Harveian orator of the Royal College of Physicians, which also awarded him its Bayly medal.

The Mackenzie era

Although Sir James Mackenzie was the key figure in shaping British cardiology, he was by inclination a general practitioner, and he worked as one for most of his professional life, despite being considered as the most famous cardiologist in the world by the European physicians visited by Arthur Hurst in 1906[25]: "Of all English physicians, the best known and most frequently quoted in Germany is probably Dr Mackenzie of Burnley, a prophet who has hardly met in his own country with the recognition which he deserves." Soon after Mackenzie started practice in Burnley in Lancashire his interest in cardiology was stimulated by unexplained tragedies among his patients, including puerperal death from heart disease.[26] He also observed unexplained irregularities in the rhythm of the heart and recognised that "if graphic records of the venous pulse, with a standard time, could be obtained, much light might be thrown upon the subject."[26] Initially unaware of the work of Marey and others, he tried to develop an instrument himelf, but "when at last I did succeed . . . both the method and the results had been already described."[26] In the first place, he applied a funnel over a pulsating vessel and connected it to a tambour and lever that inscribed the tracing on the smoked paper of a cylinder, adapting the sphygmograph introduced by Dudgeon[27] to this purpose. By 1892 he was working with an apparatus that could record several pulses simultaneously, from vein, artery, or the cardiac apex, made for him by Krohne and Sesemann in London,[26] though he did appreciate the fact that Potain had already obtained simultaneous venous and carotid tracings in 1868 and he knew that Brunton had still been working on pulse recordings in 1879. Mackenzie's monograph on the pulse in 1902[28] was extended by a series of papers in the *British Medical Journal* three years later, which made his work even more widely known,[29] but the usefulness of his techniques was greatly enhanced by the ink polygraph that he developed with Sebastian Shaw, a watchmaker in Padiham, Lancashire, in 1906.[30] Mackenzie had attributed the arrhythmia that we now recognise as atrial fibrillation to inception of the rhythm in the ventricle, later considering that it arose in the atrioventricular node; but once its true nature was established, he accepted it, though not without some reservations.[31] In 1907 he moved to London, where he was soon to encourage Lewis to undertake his electrocardiographic studies, but we should not forget that when he was a general practitioner in Burnley "distinguished men like Osler, Keith, Wenckebach, physicians, anatomists, physiologists, and others, were finding their way to Bank Parade, impressed by the importance of Mackenzie's work, and desirous of meeting the man himself. His reputation reached far, and his opinion was sought by medical men and their patients, not only from Great Britain, but also from Canada, America, Germany, and France."[25]

Mackenzie's move, at the age of 54, was not easy, and it was another five years before he was appointed to the staff of the London Hospital, though his success in private practice was immediate and great.[25] In Lewis he found a young colleague whose initial researches and editorial ventures he could stimulate. Together, during the first world war, they studied the effort syndrome. Unfortunately, his years in London and St Andrews were dogged by vascular disease[32]; indeed he had been troubled by arrhythmias—self diagnosed with his polygraph—almost from the day he devised the instrument. As early as 1893, at the age of 40, he had experienced and recorded extrasystoles. In 1901 he suffered his first attack of atrial fibrillation, which he confirmed with the polygraph; it lasted two hours. At the age of 53 he developed angina pectoris and the next year had a myocardial infarct. Subsequently he had more severe angina and recurrent episodes of atrial fibrillation and his last years were clouded by worsening vascular disease.

Mackenzie had many distinguished disciples: Lewis was too independent to fall into this category. Two are now singled out, though many members of the Cardiac Club as well as others could fall into this category. John Hay of Liverpool (1873–1959)[33] fell under Mackenzie's spell and through him met Wenckebach when he came over to visit; Hay later spent some time in Groningen before being given special responsibility for cardiac patients in Liverpool. Not surprisingly, Hay's contributions included the study of atrioventricular conduction. Another, better known, pupil, Sir John Parkinson, contributed in many ways, not the least being the systematic analysis that he carried out with Evan Bedford of the role of the electrocardiograph in the diagnosis of cardiac infarction.[34] Nowadays he is probably most often recalled as one of the co-authors of the famous paper on pre-excitation.[35]

Sir Thomas Lewis

Lewis's key role in modern British cardiology, and the importance attached to his work by Einthoven, have been amply documented.[36-38] Lewis (1881–1945) systematically analysed arrhythmias with the electrocardiograph, established the Journal *Heart* (which he edited until 1944, its name having been changed to *Clinical Science* in 1933), investigated the effort syndrome, and was the first chairman of the Cardiac Club when it was established in 1922. His interests shifted into other aspects of clinical investigation once he had published the third edition of his *Mechanism and Graphic Registration of the Heart Beat* in 1925. Lewis welcomed the new *British Heart Journal* when it first appeared fifty years ago,[39] thirty years after he had started his own journal. Yet despite his expertise in electrocardiography, early personal studies of the effects of coronary artery ligation in dogs, and awareness of the studies by James B Herrick and Fred M Smith on the electrocardiographic changes produced clinically and experimentally by coronary artery occlusion, Lewis never used the electrocardiograph to diagnose coronary artery disease.[40] This could not have been expected of Mackenzie, whose personal studies were confined to the polygraph and who practised before the electrocardiograph was used to elucidate coronary artery disease; Howell suggests that Lewis's analytical processes were based on the polygraph, too.[40] Both men suffered from chronic coronary artery disease and died of myocardial infarction. Although Parkinson, who became Mackenzie's physician[32] was actively investigating the use of the electrocardiograph in cardiac infarction, there is no evidence that Mackenzie underwent electrocardiography; in 1927, when Lewis suffered his first cardiac infarct, the diagnosis was confirmed with tracings (A Hollman, personal communication). Though both men were intense and dedicated to their work, they were also able to relax—Mackenzie at golf and Lewis at photography and bird watching, hobbies that he shared with Frank Wilson, the American who fortunately was ready to take up the challenge just as Lewis was withdrawing from electrocardiography.

A look at Lewis's publications shows the many collaborators with whom he worked over the years, and hints at the international influence that he wielded. But one example of an early association, with a physician who played no major role in cardiology, has links with contemporary practice that were impossible to envisage then. Alfred Goodman Levy (1866–1954) became consultant physician to the City of London Hospital for Diseases of the Chest in 1912. Although in later life he was a very staid individual, he had spent four very adventurous years in Matabeleland soon after completing his medical studies.[41] When he returned to London he obtained higher qualifications and then investigated one of the pressing problems of the time—death from chloroform anaesthesia. Ventricular arrhythmias with chloroform had already attracted the interest of John MacWilliam, the Aberdeen physiologist, who had studied ventricular fibrillation since 1887, and who was a steadfast friend to Mackenzie.[42] Levy had already shown that arrhythmias occurred during light rather than heavy anaesthesia with chloroform. Fresh studies, made with Lewis, using the electrocardiograph, showed that anaesthesia with low tensions of chloroform when combined with small amounts of intravenous adrenaline caused ventricular fibrillation.[43] This was half a century before Sir James Black introduced β adrenergic blockers,[44] which have specific antiarrhythmic properties.

Long after he had given up electrocardiography, Lewis remained a major figure in cardiology, writing *Diseases of the Heart* in 1933. His best known international disciples had worked with him in the two decades encompassing the first world war, but he attracted visitors long afterwards. George Burch, who was to be so important in American cardiology, had arranged to spend two years with him from September 1939 but this was thwarted by the outbreak of the second world war just as he was about to leave New Orleans for London (unpublished letter to H B Burchell). Burch subsequently paid several visits to Britain and attended meetings of the British Cardiac Society. Some of the features of the Association of University Cardiologists, of which he was a founder, reflect his British experience; but the constitution of the association was actually based on that of the Association of University Radiologists in the United States (N P DePasquale, personal communication).

Where next?

It would be tempting to bring the story up to date, but that would be at the expense of the opportunity for historical reflection. That neither Mackenzie nor Lewis considered themselves cardiologists as we use the term is clear. Mackenzie not only emphasised the importance of general practice but left London to establish the Institute for Clinical Research in St Andrews that was intended to study disease in the community. Lewis changed interests and investigated pain perception and vascular reactions. But they were the cardiologists of their day and recognised as such then and now. Their immediate associates and successors declared an exclusive interest in cardiology in private practice; but in hospital work, in London and the provinces, they were usually general physicians with an interest in cardiology, perhaps with responsibility for its key investigative tool, electrocardiography. This certainly applied to most, though not all, of the original members of the Cardiac Club, established in 1922 and consisting of 15 physicians who were consultants to the Ministry of Pensions on cardiac disability in former soldiers.[45] Howell points out that the members of the Club wrote little on cardiology, and contributed little by way of research.[46] This should not surprise us because they were established consultants, all but three were over 40, and many of them had already written papers, often on arrhythmias analysed with the polygraph and electrocardiograph. Though they may have written little on cardiological matters subsequently, they laid the foundation for their successors to do so, by creating the British Cardiac Society in 1937[47] and the *British Heart Journal* two years later. As I have already remarked,[48] over half (12) of the 23 original articles published in the first volume of the *British Heart Journal* involved the electrocardiograph. Thus the technological advances that produced electrocardiography were indeed crucial to the development of the specialty. As Lawrence points out, "Cardiology as an institutionalized medical speciality did not exist in Britain until after the Second World War."[14] It was during that war that cardiac catheterisation was introduced in the United States by Cournand and soon used in Britain.[49] Cardiac catheterisation helped delineate the specialty of cardiology more clearly, but, as with electrocardiography, an important immediate effect was to clarify symptoms and physical signs[50]; and it did, of course, put the development of cardiac surgery on a secure basis. It will not be long before the impact of such interventions, and of some of their practitioners and exponents, can be assessed—but that time is yet to come.

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Br Heart J 1989;62:235

Relations between members of the British Cardiac Society and industry

Advances in the treatment of hypertension, heart failure, and, more recently, coronary disease and hypercholesterolaemia, have resulted in huge markets and huge investments in research. Physicians and research scientists often fulfil several roles—as advisers to the industry, as prescribers to their patients, or as advisers to the National Health Service and government.

This may give rise to problems. On the one hand we are encouraged to maintain our independence from the pharmaceutical industry, so that there are no conflicts of interest in the advice we give; on the other, universities and government encourage links between universities and industry by consultancy work.

Conflicts in postgraduate education

There is a paucity of National Health Service and university funding for postgraduate education in an era of increasingly squeezed National Health Service resources. It is unrealistic to ignore the huge dependence of postgraduate tutors on the pharmaceutical industry for the support of continuing postgraduate training of general practitioners, consultants, and trainee physicians. The same dependence is evident, particularly in national and international congresses, in the postgraduate education of cardiologists.

How can the effects of these conflicts be mitigated?

CONSULTANCIES, HONORARIA

Individuals should not be discouraged from acting as consultants to industry, whether pharmaceutical companies, biomedical engineering, or the private health care sector.

Honoraria for consultancies, lecturing, or service on advisory boards should be clearly appropriate to the work performed and personal inconvenience. The payment should be open and direct, and not indirect in the form of perquisites, whether entertainment for individuals or their relatives, or gifts. (All may lead to difficulties with the Inland Revenue.)

Where there is a continuing arrangement with a company (as a consultant or a member of an advisory board), the consultancy commitment in terms of time and level of payment should be notified (in confidence) to the appropriate local body, such as academic board or District Health Authority. In any publications and reports the consultancy or support should be acknowledged as a footnote.

EDUCATION

Physicians and industry should plan the content of meetings together. Chairman or postgraduate tutors should avoid agreeing to a "fait accompli". Before agreeing to take part in a meeting it is wise to ask:

(a) who are the other speakers?
(b) what is the purpose of the meeting?
(c) what is the audience?
(d) is the meeting wholly or partly sponsored, and by which company?

The most successful advertising is that based on sound factual exploitation of the truth. It is not in the industry's long term advantage to suppress adverse effects or promote unsustainable claims.

The British Cardiac Society considers that a precise code of practice would be too rigid and would not as a result command respect. The society encourages the principle of open disclosure of relations between industry and the profession. Individuals should ask themselves "Would I be embarrassed if the invitation or payment became public knowledge?"

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Book review

Mountain medicine

High Altitude Medicine and Physiology. Michael P Ward, James S Milledge, John B West (pp 515; £50·00). London: Chapman and Hall Medical, 1989. ISBN 0412290103.

This sizeable book presents a comprehensive and up to date account of high altitude medicine and physiology by authors who over the past 25 years have been members of several scientific and mountaineering expeditions to extreme altitudes, mainly in the Himalaya. Thus they have learned about the uncomfortable and often dangerous practicalities of life on the mountainside the hard way. At the same time they have been able to apply scientific techniques rigorously to the study of the disturbed physiology and acute illnesses of exposure to high altitude. As a result each has made distinguished contributions and this experience over a lifetime is made available in this volume.

In the preface the authors record that they worked together for several months at an altitude of 5800 m (19 000 ft) during the 1960–1961 Himalayan Scientific and Mountaineering Expedition in the Everest region. This indicates the main thrust of the book, which is the detailed physiological and clinical study of lowlanders "striving to reach the loftiest summits of the earth" in the words of Whymper. The early chapters on the physiological adjustments to exposure to this inhospitable environment characterised by hypobaric hypoxia and cold are excellent. Some of the most interesting sections derive from investigations carried out at extreme altitude during the 1981 American Medical Research Expedition to Everest, particularly those concerned with sleep and periodic breathing at these great altitudes and the residual impairment of the central nervous system after descent. The chapter on the endocrine system at high altitude is most interesting, particularly the sections on the renin-angiotensin-aldosterone system. Growing points such as the role of atrial natriuretic peptide in life at high altitude are considered.

The clinically orientated chapters in the second half of the book deal with acute mountain sickness and its malignant complications (pulmonary and cerebral oedema), fitness for altitude, mountain performance, hypothermia, frostbite, and accidents and emergencies. These titles indicate the emphasis of the book on the adjustment of the high altitude climber to very high altitudes.

Less attention is paid to the features and diseases of the native highlander in his mountain environment, who undertakes not a brief foray into high altitude but is born into and spends his entire life at 3000 to 4500 m. Though this range is lower than that experienced by high altitude climbers, it is the permanent domicile of millions throughout the world. As a result one senses that chapters on such subjects as Monge's disease do not carry the authority that comes from personal experience and this is probably a reflection of the fact that the authors' work has been predominantly in the Himalaya rather than in the Andes. The chapter on Monge's disease is illustrated by only one line diagram without any halftones so that it is impossible to form a clear picture of the features of chronic mountain sickness. The volume as a whole could be improved by more halftone illustrations. Because the book places less emphasis on the features and diseases of the native highlander it follows that the pathology of high altitude is not considered in much detail. This has led to some important omissions such as the lack of any description of the condition of the recently reported subacute infantile mountain sickness found in infants of Han origin ascending to higher altitudes in Tibet. This is unfortunate because this disease is of considerable theoretical interest as it seems to be the human counterpart of brisket disease in cattle.

The book is marred by a considerable number of typographical errors, including an insensitivity to Spanish, which is unfortunate because many of the authorities who have made important contributions to this subject are Peruvian, like Peñaloza and Saldaña who have both lost their tilde. DONALD HEATH

Br Heart J 1989;62:237–9

Correspondence

Radionuclide measurements of diastolic function for assessing early left ventricular abnormalities in the hypertensive patient

Sir,
Caruana *et al* reported changes in the radionuclide measurements of diastolic cardiac function in hypertensive patients (1988;59:218–26). Although I agree completely with their findings I am concerned about the interpretation of these findings. In their summary they state that "The occurrence of diastolic abnormalities when systolic function is still normal may mark an early stage in the development of hypertensive heart failure." This statement, and the introduction to the paper suggest the presence of an intrinsic cardiac problem, evident as a reduced compliance.

No proof for such a cardiac abnormality is yet available. On the contrary, it has been shown that the changes in the indices of diastolic function and their "improvement" by certain drugs are secondary to alterations in loading conditions, as well as to other factors such as the sympathetic tone.[1 2] The finding that the impairment of indices of diastolic function precedes even the development of myocardial hypertrophy[3] also supports the hypothesis that these changes are secondary to alterations in loading conditions. I believe that this point should have been emphasised.

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3 Antonelli G, Sabato G, Tota F, *et al.* Left ventricular diastolic filling in subjects with hypertensive pressure response to handgrip and normal myocardial mass [Abstract]. *Eur Heart J* 1988;9(suppl 1):81.

This letter was shown to the authors, who reply as follows:

Sir,
In our study we carefully defined and validated radionuclide techniques for measuring diastolic left ventricular function. We also showed that the peak filling rate did not separate controls from those with hypertension as previously suggested.[1 2] There was considerable overlap of indices of diastolic function between controls and patients with hypertension; this was not found between controls and those with chronic stable angina.[3] Thus the finding of diastolic dysfunction in hypertensive patients should be interpreted with caution.

Indeed, we feel that the last paragraph of our summary is valid. The hypertensive group was divided into two, one with normal and the second with abnormal electrocardiographic changes. Blood pressure was not significantly different in these two groups. Despite equal "loading" conditions, patients with abnormal electrocardiography had worse diastolic left ventricular function. Therefore, some other factor other than hypertension produced these abnormal findings. In the absence of clinically significant coronary artery disease one may, therefore, postulate that some hypertensive patients are liable to intrinsic diastolic left ventricular dysfunction, which may be related to calcium overload and left ventricular hypertrophy. Finally, Dr Schneeweiss's comments are further invalidated, because he alludes to a paper where alterations in diastolic function were induced by short term intervention with drugs in normal volunteers[4] rather than in hypertensive patients. This fact has little or no bearing on our study.

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Plasma atrial natriuretic peptide in patients with acute myocardial infarction: effects of streptokinase

Sir,
Phillips *et al* studied plasma concentrations of atrial natriuretic peptide after acute myocardial infarction (1989;**61**:139–43). They did not report a significant correlation between plasma concentrations of atrial natriuretic peptide and peak concentrations of creatine kinase, which is an index of the severity of infarction. In their study, blood was sampled for the determination of atrial natriuretic peptide on the morning after admission, which was, as we understand, at least 0–32 hours after the onset of symptoms.

The exact timing of blood sampling for atrial natriuretic peptide is of great importance. We measured atrial natriuretic peptide concentrations at fixed times during 48 hours in 38 patients who were admitted to the coronary care unit within 4 hours 25 minutes after the onset of symptoms.[1] Three hours after admission, the mean atrial natriuretic peptide concentration was significantly lower than it was on admission. Thereafter, atrial natriuretic peptide concentrations rose till 15 hours after admission. Both the atrial natriuretic peptide value on admission and the individual mean atrial natriuretic peptide value during the study period of 48 hours were significantly correlated with the maximum creatine kinase value.

We agree with the hypothesis of Phillips *et al* that acute myocardial dysfunction after myocardial infarction, by raising atrial pressures, causes a release of atrial natriuretic peptide from atrial storage granules. The ensuing decrease in atrial natriuretic peptide concentrations found in our study may possibly be attributed to depletion of these storage granules. At this stage, circulating atrial natriuretic peptide concentrations will decrease despite increased intracardiac pressures. Subsequently atrial natriuretic peptide is synthesised at a greater rate causing its concentrations in the blood to rise again. Our results imply that the correct interpretation of atrial natriuretic peptide values after acute myocardial infarction depends on the timing of blood sampling.

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‡E J P Lamfers,
‡P M J Corten,
†P W C Kloppenborg,
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Reference

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This letter was shown to the authors, who reply as follows:

Sir,
We found that plasma concentrations of atrial natriuretic peptide were higher in patients with acute myocardial infarction who were not treated with thrombolysis than in similar patients admitted with non-ischaemic chest pain and patients with myocardial infarction treated with streptokinase. Patients with ischaemic chest pain had intermediate concentrations of atrial natriuretic peptide. The finding of raised plasma atrial natriuretic peptide in the acute stages of myocardial infarction was confirmed by Tan *et al* and others.[1]

Both Tan *et al* and Svanegaard *et al*[1] found that initially raised plasma atrial natriuretic peptide concentrations in patients with myocardial infarction fell soon after admission. The extent of the fall found by Tan *et al* is unclear. Despite this fall plasma atrial natriuretic peptide concentrations remained raised in the patients reported by Svanegaard *et al* especially when cardiac failure was present.[1] This fall in plasma atrial natriuretic peptide may reflect the beneficial effect of treatment (for example, bed rest, diuretics, glyceryl trinitrate, analgesia, thrombolysis) on left ventricular function as well as the initial depletion of atrial storage granules. Not enough detail is given by these other workers for us to comment further on the cause of the fall. Depletion of storage granules, however, seems to be an unlikely mechanism, because plasma atrial natriuretic peptide concentrations fell in all patients irrespective of the initial atrial natriuretic peptide concentration.

We agree with Tan *et al* that both the timing of the blood sample and the degree of infarction are important variables in interpreting plasma atrial natriuretic peptide concentrations. Indeed we found that in an experimental model of myocardial infarction the concentration of plasma atrial natriuretic peptide correlated well not only with the haemodynamic changes but also with the degree of infarction measured histologically.[2] In this experimental model it was also possible to show an inverse relation between plasma atrial natriuretic peptide and atrial atrial natriuretic peptide. That we did not find a relation between peak concentrations of cardiac enzymes and plasma atrial natriuretic peptide in our human study was probably the result of the confounding effects of streptokinase treatment, which increased peak enzyme concentrations but lowered plasma atrial natriuretic peptide, and the inclusion of patients with ischaemic chest pain who had normal concentrations of cardiac enzyme but intermediate concentrations of plasma atrial natriuretic peptide, as well as the variable times of blood sampling (7–32 hours after admission). This underscores the difficulty of studying and interpreting the dynamics and mechanism of atrial natriuretic peptide release in patients with heart disease.

The finding of raised concentrations of plasma atrial natriuretic peptide during the acute stage of myocardial infarction before appreciable volume expansion could occur suggests that acute myocardial dysfunction alone may raise plasma atrial natriuretic peptide concentrations, probably by reducing ventricular compliance and increasing atrial pressures. This may be a beneficial homoeostatic response that acts to reduce cardiac preload and limit salt and water retention during the acute stages of myocardial ischaemia.

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Pulmonary capillary haemangiomatosis

Sir,

A registry is being formed to document and study cases of pulmonary capillary haemangiomatosis, an exceptionally rare disease (only eight cases have been described) that leads to proliferation of capillaries in the lung and pulmonary hypertension. Anyone knowing of patients with this disorder is asked to contact either (1) CANADA and EUROPE: Dr David Langleben, Jewish General Hospital, 3755 Côte St Catherine, Montreal, Quebec H3T 1E2, Canada; or (2) USA, MIDDLE EAST, and ORIENT: Dr Carl W White, Division of Pulmonary Disease, The Children's Hospital, 1956 East 19th Avenue, Denver, Colorado 80218-1088, USA. Strict confidentiality will be maintained and a newsletter will be circulated to all contributors.

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Canada.

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Notices

British Cardiac Society

The Annual General Meeting will take place in Torquay on 22 to 25 May 1990.

Nuclear cardiology

The British Nuclear Cardiology Group is holding a meeting in the Lecture Theatre of the National Heart and Lung Institute, Dovehouse Street, London SW3 on 3 November 1989. Further informaton: Dr Ann Tweddel, Department of Medical Cardiology, Royal Infirmary, 10 Alexandra Parade, Glasgow G31 2ER.

Cardiac radiology

The Bristol Cardiac Radiology Course is an intensive one day meeting to update radiologists and others interested in the imaging of the heart in all aspects of cardiac imaging. It will be held on 18 November 1989. For further information contact Dr G G Hartnell, Department of Radiodiagnosis, Bristol Royal Infirmary, Bristol BS2 8HW. Telephone 0272-230000 Ext 2130.

Cardiology for the clinician

A course on Cardiology '90—Pearls for the Clinician will be held in La Jolla, California on 25 to 27 January 1990. For further information write to Nancy Donegan, Deverman and Associates, 7777 Alvarado Road, Suite 110, La Mesa, California 92041, USA.

Intensive care and emergency medicine

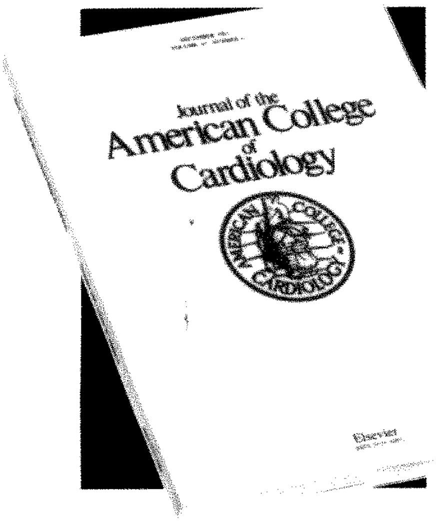
The 10th International Symposium on Intensive Care and Emergency Medicine will be held in Brussels on 27 to 30 March 1990. For further information write to Professor J L Vincent, Department of Intensive Care, Erasme University Hospital, Route de Lennik 808, B-1070 Brussels, Belgium.

Electrocardiology and vectorcardiography

The XVII International Congress on Electrocardiology and XXXI International Symposium on Vectorcardiography will be held in Florence on 27 to 29 September 1990. Information from the Organising Secretariat, Via G Modena 19, 50121 Florence, Italy.

Correction

Impact of a policy of direct admission to a coronary care unit on use of thrombolytic treatment *J M A Burns, K J Hogg, A P Rae, W S Hillis, F G Dunn*—We regret that there is an error in this article published in the April issue (volume 61: pages 322–5). In the Summary, the third sentence should have read "Those admitted via the accident and emergency department at the same hospital reached the coronary care unit 1 h 32 min after being seen by the general practitioner whereas the patients admitted directly took only 43 minutes".



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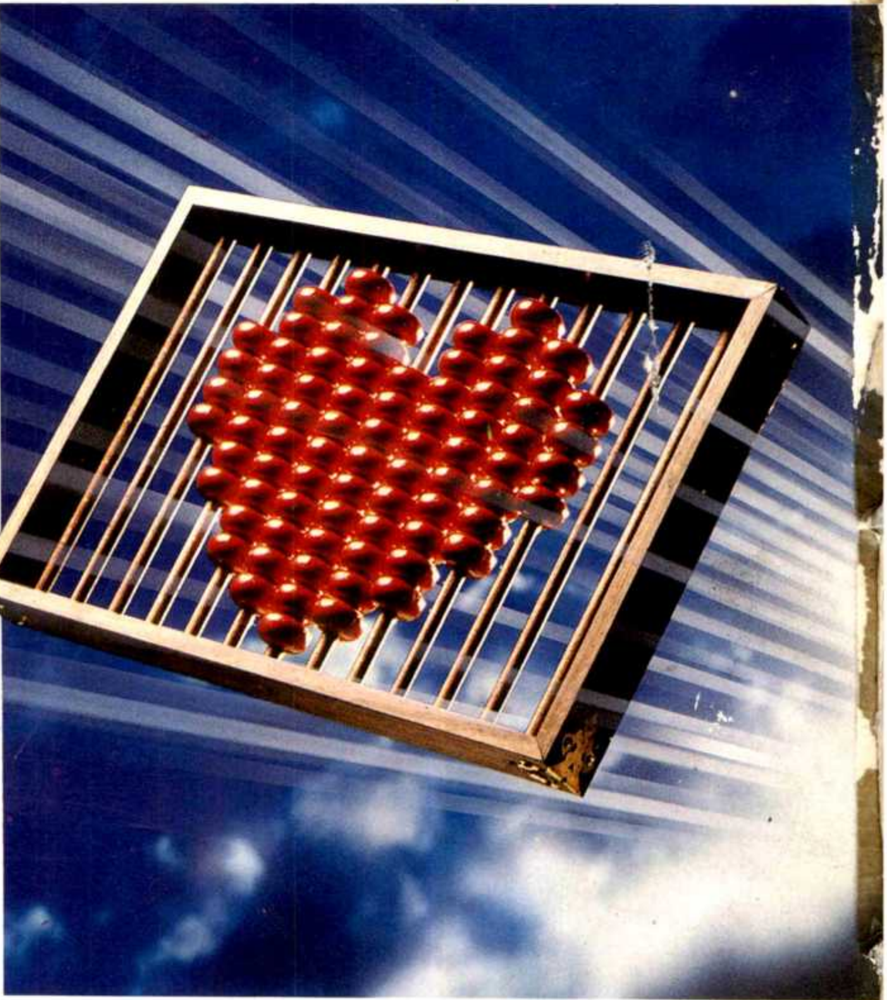

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